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IN RE APPLICATION OF	:
KANAME KAWASUGI	: EXAMINER: WEDDINGTON, K. E.
SERIAL NO: 10/572,557	:
FILED: MARCH 17, 2006	: GROUP ART UNIT: 1614
FOR: MEDICINAL COMPOSITION	:

DECLARATION UNDER 37 C.F.R. 1.132

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

SIR:

I, Kaname Kawasugi, hereby declare:

1. I am the named inventor on the above-identified U.S. patent application. As a result, I am knowledgeable about its contents and the claims that have been filed.

2. I understand that the U.S. Patent Office has maintained that the claims which define a medicinal composition with an insulin resistance-improving drug and vitamin B_1 or derivative thereof in an amount effective for inhibiting at least one side effect of said insulin resistance-improving drug would have been obvious.

3. Specifically, the U.S. Patent Office relies on what is described in the previously cited US 4,687,777 (Meguro et al), US 5,002,953 (Hindley), FR 2,832,064 (Gerard et al), US 6,251,926 (Momose et al) and US 6,166,219 (Yamasaki et al) in view of US 5,977,073 (Khaled) or US 6,660,293 (Giordano et al) with a newly cited publication by Tamai, *Japanese J Clin Med* 57(10):200-203, 1999.

4. As I understand the rejection, referencing the Tamai publication, it is that vitamin B_1 is a well-known supplement to reduce insulin requirements as supposedly discussed in the cited Khaled and Giordano documents.

5. The insulin resistance-improving drugs pioglitazone, rosiglitazone and CS-011 were known as shown in some of the publications cited by the Patent Office.

6. However, what is described in Khaled and Giordano with regards to vitamin B_1 or derivatives thereof is not particular informative as to the inclusion of vitamin B_1 in compositions with insulin resistance-improving drugs.

7. Khaled discusses treatment of an immune disorder with a nutrient composition which may contain thiamine and as one of such disorders, diabetes is mentioned in column 3. Giordano et al a prophylactic and therapeutic supplementation of nutrition that may contain thiamine, and may be administered to patients with various diseases or disorders, including poorly controlled diabetes (paragraph bridging columns 1 and 2).

8. However, diabetes and insulin therapy (and the patients that receive such therapy) as is the case with Khaled and Giordano is different from insulin sensitizer therapy and as such the Khaled and Giordano patents are not relevant to the question of whether one would have included vitamin B1 with insulin resistance-improving drugs.

9. In the rejection, the newly cited Tamai publication also is not relevant to the question of whether one would have included vitamin B1 with insulin resistance-improving drugs. In fact, it seems there is a fundamental misunderstanding about what is described in the Tamai reference.

10. By way of background, diabetic patients receiving insulin therapy (like those that are targeted in Tamai, Khaled and Giordano) are not the same patients that would receive therapy with insulin-sensitizer drugs, generally.

11. An insulin-resistance improving (Insulin sensitizer) drug is used when, although the endogenous insulin is secreted, the clinical condition is such that the muscle sensitivity is deteriorating. In contrast, insulin therapy is used in the clinical condition such as type 1 diabetes and depletion of endogenous insulin. It is called the "Insulin sensitizer" but the concept is different. Insulin therapy patients generally do not take insulin sensitizer drugs, and patients taking insulin sensitizer drugs generally do not have insulin therapy. (see attached documents, Harrison's Principles of Internal Medicine, 15th Ed, Braunwald *et al.* (Ed.), McGraw-Hill, pp. 2109-2111, 2123, 2129-2135 and the underlined portions therein; *N Engl J Med* 358;3 January 2008 "Management of Type 2 Diabetes; McMahon *et al.*, *N Engl J Med* 356;5 February 2007 "Inhaled Insulin for Diabetes Mellitus"; and the attached printouts from the American Diabetes Association webpage (www.diabetes.org) which outlines the conditions, treatments, and drugs used to combat those disorders).

12. Indeed, the European Agency for the Evaluation of Medicinal Products considers insulin therapy and insulin sensitizer drugs (thiazolidinediones including rosiglitazone and pioglitazone) are contraindicated (e.g., see the discussion of thiazolidinediones, a class of insulin sensitizers, in the sentence bridging pages 1114-115 in Järvinen *N Engl J Med* 351;11 September 2004). Contraindicated means "to make (a treatment or procedure) inadvisable" (http://www.merriam-webster.com/dictionary/contraindicated).

13. Tamai refers to reduced usage of insulin, i.e., less insulin in an insulin administration protocol, but this discussion does not link to the reduction of side-effects due to insulin-resistance improving drugs. Thus, at best Tamai only suggests the relationship between vitamin B1 and diabetic peripheral neuropathy (treated with insulin not with insulin sensitizers).

14. Further, my reading of Tamai leads to a conclusion that Tamai does not actually link vitamin B1 supplementation with insulin therapy but rather vitamin B6 with insulin

therapy, much like that which is described in the Harrison's textbook (see pp. 2123, col. 1, paragraph titled "Treatment").

15. Tamai was published in Japanese and I am fluent in Japanese and therefore have reviewed its entire contents. The Patent Office seems to rely on the portions of the Abstract that mentions plasma vitamin B1 and then in a second portion of the English Abstract suggests administering vitamins to diabetic patients.. My view is reliance on this Abstract is misplaced and when the entirety of Tamai is reviewed, it does not appear to me that Tamai ever correlates B1 with insulin and the use of B1 in diabetic patients but rather focuses on B6 in that manner.

16. The focal description in the English abstract has a counterpart in the "Conclusion" part of the Japanese description. In the description about vitamin B6, Tamai stated that "in the second half of pregnancy the amount of insulin increases, but B6 deficiency during pregnancy is related to insulin resistance due to pregnancy." There is no other description which implies the reduction of necessary amount of insulin. Moreover for women who become pregnant, rosiglitazone and pioglitazone are classified as pregnancy category C (relatively contraindicated and they should be used sparingly, if at all-see Järvinen 2004 p1112). This indicates to me that the cited portion of the English abstract is not directed to vitamin B1 but B6.

17. In the "Conclusion" part, Tamai stated that, in recent years, there has been some device not only to improve the secondary-generated vitamin deficiency but also to reduce the amount of insulin required, or to prevent improve the pharmacological action expected to actively administration, and reduce the amount of insulin required, or to prevent complications hoping for the improvement of pharmacological action. But it is clear that in the underlined sentence, Tamai is referring to B6.

18. Reducing the amount of insulin required for "The insulin therapy (injections)" diabetes patients and decreasing the side effects of insulin sensitizer medicines are problems of completely different dimension.

19. Insulin therapy is a treatment for patients of type 1 diabetes and advanced type 2 diabetes, and for those uncontrollable by oral hypoglycemic agent. It is not for patients who take insulin sensitizer drugs commonly. Again, insulin therapy is a treatment for patients who have a lack of endogenous insulin such as type 1 diabetes generally, while insulin sensitizer drugs are generally for those whose endogenous insulin secretion is sufficient, but their sensitivity to insulin is decreased.

20. The decreased amount of insulin required in Tamai is the amount of insulin needed in insulin therapy (injections). Also, in Tamai decrease of diabetic complications means common complications of diabetes, including peripheral neuropathy but not side-effects due to insulin sensitizer drugs.

21. Therefore, one would not have derived from this information coupled with what is described in the other documents cited by the Patent Office (e.g., Khaled and Giordano) to combine B1 and insulin sensitizer drugs.

22. Tamai's description regarding the reducing amount of insulin is an object for vitamin B6 but not vitamin B1. Further, reducing the amount of insulin in insulin therapy, and easing the side effects of endogenous insulin are completely different. Thus, the statement by the Patent Office in the rejection on page 3, second paragraph that Vitamin B1 is used with the anti-diabetic agent to reduce insulin requirement as well-known in the art relying on Tamai is a mistake.

23. As Khaled, Giordano and Tamai are all primarily concerned with diabetes (which is treated with insulin) but not patients using insulin sensitizer drugs, I do not agree with the presumption outlined in the last paragraph on page 3 of the Action that combining

information related to insulin therapy and insulin sensitizer therapy is something that one would have done, particularly when the recognition in the field is not to do so.

24. Therefore, that the side effects caused by the administration of an insulin resistance-improving drug to a patient can be inhibited when the drug is administered simultaneously with vitamin B_1 or a derivative thereof could not have been reasonably predicted based on what is described in the totality of the publications cited by the Patent Office and the knowledge and experience I have in this field.

25. The undersigned declares further that all statements made herein of his/her own knowledge are true and that all statements made on information and belief are believe to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

Kaname Kawasugi

Kaname Kawasugi, M.D., Ph.D.

June 24, 2008

Date

REVIEW ARTICLE

DRUG THERAPY

Thiazolidinediones

Hannele Yki-Järvinen, M.D., F.R.C.P.

From the Division of Diabetes, Department of Medicine, University of Helsinki, Helsinki. Address reprint requests to Dr. Yki-Järvinen at the Division of Diabetes, Department of Medicine, P.O. Box 340, 00029 HUS Helsinki, Finland, or at ykijarvi@cc.helsinki.fi.

N Engl J Med 2004;351:1106-18.

INSULIN RESISTANCE BOTH PRECEDES AND PREDICTS TYPE 2 DIABETES MELLITUS.[1] Although exercise and weight loss ameliorate insulin resistance and may in some cases prevent or delay onset of the disease,[2] therapy that combats insulin resistance in those who fail to change their lifestyle is needed. Current pharmacologic approaches are unsatisfactory in improving such consequences of insulin resistance as hyperglycemia, diabetic dyslipidemia, abnormal coagulation and fibrinolysis, and hypertension,[3] each of which may require the use of at least one medication. Thus, the development of drugs targeted to reverse insulin resistance is important. The insulin-sensitizing thiazolidinediones, which are selective ligands of the nuclear transcription factor peroxisome-proliferator–activated receptor γ (PPARγ),[4] are the first drugs to address the basic problem of insulin resistance in patients with type 2 diabetes. Furthermore, this class of agents may have a role in treating patients with nondiabetic insulin-resistant conditions. This review briefly describes the current understanding of the mechanisms of action of thiazolidinediones and focuses on their use as hypoglycemic therapies in patients with type 2 diabetes.

THE SUPERFAMILY OF PEROXISOME-PROLIFERATOR–ACTIVATED RECEPTORS

The peroxisome-proliferator–activated receptors (PPARs) are a subfamily of the 48-member nuclear-receptor superfamily[5] and regulate gene expression in response to ligand binding.[6,7] Various fatty acids serve as endogenous ligands for PPARs, whereas some members of the superfamily (farnesoid X receptors) bind bile acids and others (liver X receptors) bind oxysterols.[5] Three PPARs, designated PPARα, PPARδ (also known as PPARβ), and PPARγ, have been identified to date.

After ligand binding, PPARs undergo specific conformational changes that allow for the recruitment of one coactivator protein or more.[8] Ligands differ in their ability to interact with coactivators, which explains the various biologic responses observed.[6,7,9-11] PPARs regulate gene transcription by two mechanisms (Fig. 1). Transactivation is DNA-dependent and involves binding to PPAR response elements of target genes and heterodimerization with the retinoid X receptor.[8] A second mechanism, transrepression, may explain the antiinflammatory actions of PPARs. It involves interfering with other transcription-factor pathways in a DNA-independent way.[9]

PPARα is expressed predominantly in the liver, heart, and muscle, as well as in the vascular wall.[7] Fibrates such as fenofibrate, bezafibrate, ciprofibrate, and gemfibrozil act as full or partial PPARα agonists. In general, PPARα activation enhances free fatty acid oxidation, controls expression of multiple genes regulating lipoprotein concentrations, and has antiinflammatory effects (Fig. 2). PPARα agonists prevent or retard atherosclerosis in mice and humans.[12-14]

PPARδ is expressed in many tissues, with the highest expression in the skin, brain, and adipose tissue. In mice in which PPARδ is ablated (PPARδ null mice),[15] these tissues display alterations such as delayed wound closure and diminished myelination.

PPARγ is expressed most abundantly in adipose tissue but is also found in pancreatic beta cells, vascular endothelium, and macrophages.[8,16] Its expression is low in tissues that express predominantly PPARα, such as the liver, the heart, and skeletal muscle. The discovery of PPARγ as the target for thiazolidinediones was followed by large-scale clinical trials of several agents.[17-27] In January 1997, the first thiazolidinedione, troglitazone, was approved as a glucose-lowering therapy for patients in the United States with type 2 diabetes. Troglitazone was subsequently withdrawn from the market, in March 2000, because of hepatotoxicity. The two currently available PPARγ agonists, rosiglitazone and pioglitazone, were approved in the United States in 1999.

MECHANISM OF ACTION OF THIAZOLIDINEDIONES

INSULIN SENSITIVITY AND SECRETION

Thiazolidinediones consistently lower fasting and postprandial glucose concentrations as well as free fatty acid concentrations in clinical studies.[28-31] Insulin concentrations also decrease in most studies.[28-31] Such changes indicate that thiazolidinediones act as insulin sensitizers, which has been confirmed by direct measurements in in vivo studies in humans. For example, treatment of nondiabetic subjects or those with type 2 diabetes for three to six months with troglitazone, rosiglitazone, or pioglitazone increases insulin-stimulated glucose uptake in peripheral tissues.[28,30,32-34] In similar studies, thiazolidinediones increase hepatic insulin sensitivity (the ability of insulin to suppress endogenous glucose production) and insulin sensitivity in adipose tissue (measured from the ability of insulin to suppress free fatty acid concentrations).[30] In addition, insulin secretory responses, even after adjustment for an improvement in insulin sensitivity, have increased in subjects with impaired glucose tolerance[35] and type 2 diabetes.[36] Somewhat paradoxically, these improvements are generally accompanied by weight gain and an increase in the subcutaneous adipose-tissue mass.[30,32,33,37,38]

ENHANCEMENT OF INSULIN SENSITIVITY

PPARγ is essential for normal adipocyte differentiation and proliferation as well as fatty acid uptake and storage. Thiazolidinediones increase the number of small adipocytes and the subcutaneous adipose-tissue mass in studies in animal models.[11,32,39] These observations, plus the high level of PPARγ expression in adipose tissue, have led to the hypothesis that thiazolidinediones exert their insulin-sensitizing actions either directly (the "fatty acid steal" hypothesis) or indirectly, by means of altered adipokine release, modulating insulin sensitivity outside adipose tissue. According to the "fatty acid steal" hypothesis, thiazolidinediones promote fatty acid uptake and storage in adipose tissue. In this way, they increase adipose-tissue mass and spare other insulin-sensitive tissues such as skeletal muscle and the liver, and possibly pancreatic beta cells, from the harmful metabolic effects of high concentrations of free fatty acids. Thiazolidinediones thus keep fat where it belongs.

In a manner consistent with that hypothesis, thiazolidinediones lower circulating free fatty acid concentrations and triglyceride content in the liver, but not in skeletal muscle, in patients with type 2 diabetes[31,37,40-42] and lipodystrophy.[43] Metformin increases insulin sensitivity in the liver without changing its fat content in patients with type 2 diabetes,[42] and thiazolidinediones can lower fasting insulin concentrations without increasing subcutaneous fat mass in patients with lipodystrophy.[43]

In mice, targeted deletion of PPARγ in adipose tissue does not induce insulin resistance in muscle,[44] whereas muscle-specific PPARγ deletion does cause such resistance.[45] Insulin resistance in muscle is unresponsive to thiazolidinediones, implying that these agents sensitize by directly stimulating muscle PPARγ receptors.[45] Hepatic insulin resistance in mice lacking PPARγ in adipose tissue can be reversed with thiazolidinediones.[44] These data suggest that the insulin-sensitizing effects of thiazolidinediones in the liver and muscle of mice are not mediated by PPARγ receptors in adipose tissue in cases in which adipose tissue is unable to respond to these agents normally. However, the lipoatrophy that accompanies tissue-specific PPARγ deletion may make the action of PPARγ agonists abnormally dependent on PPARγ expression in other tissues. For example, rosiglitazone is able to reverse hypertriglyceridemia, hyperglycemia, and hyperinsulinemia in normal mice, whereas the drug is ineffective in lipoatrophic mice.[46] Taken together, data from knockout-mouse models support the idea that adipose tissue is the most important site for thiazolidinedione action if there are normal amounts of adipose tissue.

INDIRECT EFFECTS IN ADIPOSE TISSUE

Although thiazolidinediones may enhance insulin sensitivity by keeping fat where it belongs, indirect effects may also be involved. Gene-expression pro-

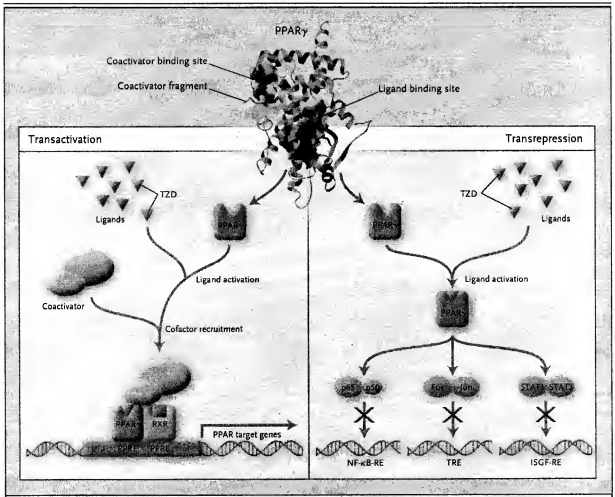

Figure 1. **Molecular Mechanisms of Biologic Responses of Thiazolidinediones.**

Peroxisome-proliferator–activated receptor γ (PPARγ) is a transcription factor activated by thiazolidinediones (TZDs). In transactivation, which is DNA-dependent, PPARγ forms a heterodimer with the retinoid X receptor (RXR) and recognizes specific DNA response elements called PPAR response elements (PPRE) in the promoter region of target genes. This results ultimately in transcription of PPARγ target genes. After ligand binding, PPARs undergo conformational changes, which lead to recruitment of cofactor proteins and coactivators. The coactivators interact with nuclear receptors in a ligand-dependent way and influence the set of genes transcribed. In transrepression, PPARs can repress gene transcription by negatively interfering with other signal-transduction pathways, such as the nuclear factor-κB (NF-κB) signaling pathway. In a DNA-binding–independent manner, STAT denotes signal transducers and activators of transcription, ISGF-RE interferon-stimulated gene factor responsive element, and TRE TPA responsive element, where TPA is a phorbol ester.

filing studies using oligonucleotide microarrays in differentiated 3T3-L1 adipocytes have indicated that rosiglitazone and pioglitazone each regulate the expression of more than 100 genes and that these genes are not identical, although they cluster together.[10] A small fraction of the established PPARγ target genes that also seem to be regulated in human adipose tissue in vitro are shown in Figure 2.[47-49] Various adipokines, such as adiponectin,[50,51] tumor necrosis factor α,[52] resistin,[53] and 11β-hydroxysteroid dehydrogenase 1, the enzyme that produces cortisol locally in adipose tissue,[11,54] are among the genes that are regulated by PPARγ agonists in rodents. Of these, adiponectin increases insulin sensitivity, and tumor necrosis factor α, resistin, and 11β-hydroxysteroid dehydrogenase 1[55] induce insulin resistance in rodents.

Adiponectin, an adipocytokine produced exclu-

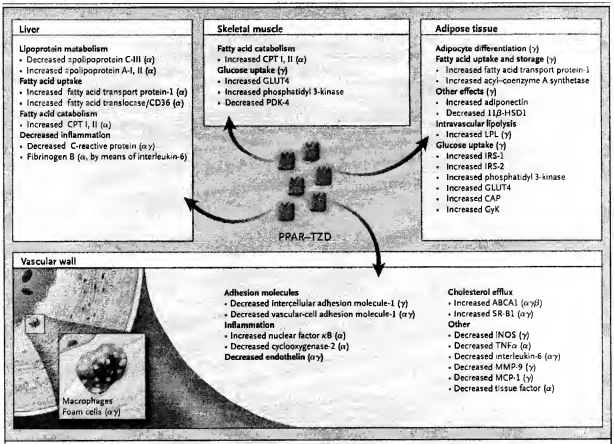

Figure 2. **Molecular Targets of PPARγ and PPARα Action.**

PPARα is expressed mainly in the liver, in skeletal muscle, in the heart (not shown), and in the endothelial cells and smooth-muscle cells of the vascular wall. It regulates genes that influence lipoprotein metabolism and fatty acid uptake and oxidation as well as production of inflammatory markers. PPARγ is expressed mainly in adipose tissue, where it regulates genes involved in adipocyte differentiation, fatty acid uptake and storage, and glucose uptake. It also stimulates intravascular lipolysis. CPT denotes carnitine palmitoyl transferase, α regulation of the gene by PPARα agonists, γ regulation of the gene by PPARγ agonists, β regulation of the gene by PPARβ (PPARδ) agonists, GLUT4 insulin-sensitive glucose transporter, PDK-4 pyruvate dehydrogenase kinase 4, HSD1 hydroxysteroid dehydrogenase type 1, LPL lipoprotein lipase, IRS insulin-receptor substrate, CAP Cbl–associated protein, GyK glycerol kinase, ABCA1 ATP-binding cassette A1, SR scavenger receptor, INOS inducible nitric oxide synthase, TNF-α tumor necrosis factor α, MMP-9 matrix metalloproteinase 9, MCP-1 monocyte chemoattractant protein 1, and TZD thiazolidinedione.

sively by adipose tissue, has both insulin-sensitizing and antiatherogenic properties in mice.[50,51] PPARγ agonists increase adiponectin expression in vitro in adipose tissue.[56] Adiponectin levels are low in patients with obesity and type 2 diabetes,[57-62] as well as in patients with lipodystrophy.[63-66] In vivo treatment with thiazolidinediones[31,56,59-61,67,68] markedly increases circulating concentrations of adiponectin, the most abundantly expressed gene transcript in human adipose tissue.[69] It is unclear whether adiponectin increases hepatic insulin sensitivity in humans as it does in mice, although plasma adiponectin concentrations correlate with liver fat content both before and after thiazolidinedione treatment in patients with type 2 diabetes.[31,42]

In the liver and in adipose tissue, 11β-hydroxysteroid dehydrogenase 1 catalyzes the interconversion of cortisone to cortisol.[70] A full-blown metabolic syndrome characterized by obesity and the accumulation of visceral fat, as well as increased concentrations of cortisol in the portal vein but not of systemic cortisol, develops in mice that overex-

press 11β-hydroxysteroid dehydrogenase 1 in adipose tissue.[55] Thiazolidinediones down-regulate 11β-hydroxysteroid dehydrogenase 1 expression in adipose tissue[54] and might thereby alleviate features of the metabolic syndrome. However, no data on the effects of thiazolidinediones on 11β-hydroxysteroid dehydrogenase 1 activity or expression in humans are available.

The many effects of thiazolidinediones in various tissues make it impossible to define the exact mechanisms underlying their insulin-sensitizing effects in vivo in humans. Data suggest that multiple mechanisms are probably involved (Fig. 3). One mechanism includes stimulation of free fatty acid storage in adipose tissue, sparing other tissues such as the liver, skeletal muscle, and possibly beta cells from lipotoxicity.[71] These drugs may also have indirect insulin-sensitizing effects, especially in the liver by means of the secretion of adiponectin from adipose tissue.

CLINICAL EFFICACY OF THIAZOLIDINEDIONES IN HUMANS

EFFECTS IN PATIENTS WITH TYPE 2 DIABETES

Rosiglitazone and pioglitazone are currently approved in most countries for the treatment of hyperglycemia in patients with type 2 diabetes, either as monotherapy or in combination with sulfonylureas or metformin. In the United States, both drugs have also been approved for use in combination with insulin, provided certain precautions are followed.

HYPOGLYCEMIC EFFECTS

Placebo-controlled studies suggest that both pioglitazone and rosiglitazone are moderately effective in achieving glycemic control (Table 1). At maximal doses, these two drugs seem to decrease glycosylated hemoglobin values on average by 1 to 1.5 percent. Thus, in a typical patient with type 2 diabetes, one may expect glycosylated hemoglobin to decrease from a value of 8.5 percent to a value of 7 percent (normal range, 4 to 6 percent). Pioglitazone and rosiglitazone decrease glycosylated hemoglobin values more than the weakest hypoglycemic drugs (e.g., nateglinide and α-glucosidase inhibitors) but slightly less than full doses of glimepiride (4 to 6 mg), glyburide (glibenclamide, 10 to 15 mg), or metformin (2 to 2.5 g).[72-74] Whether thiazolidinediones are used as monotherapy or are added to existing therapies does not seem to affect their hypoglycemic efficacy. No data are available on patient characteristics that can predict a good treatment response, and no data are available to support long-term maintenance of glycemic control with rosiglitazone or pioglitazone as compared with other existing therapies. Ongoing studies may be useful, such as the A Diabetes Outcome Progression Trial (ADOPT), which involves patients with type 2 diabetes who have not previously received treatment and who have been randomly assigned to receive rosiglitazone, glyburide, or metformin monotherapy.[75]

EFFECTS ON LIPIDS

There are no head-to-head double-blind studies comparing the effects of pioglitazone and rosiglitazone on serum lipids and lipoproteins. However, low-density lipoprotein (LDL) cholesterol levels have consistently remained unchanged when monotherapy with pioglitazone or combination therapy with pioglitazone and sulfonylurea, metformin, or insulin has been used. In contrast, increases in LDL cholesterol levels, ranging from 8 to 16 percent, have been noted in studies of rosiglitazone (Fig. 4). High-density lipoprotein (HDL) cholesterol levels have increased by approximately 10 percent with both drugs.

The effects of thiazolidinediones on triglycerides have been somewhat more variable. Decreases in triglyceride levels have been observed more often with pioglitazone than with rosiglitazone (Fig. 4). The only direct comparison of rosiglitazone and pioglitazone in an open-label trial, in 127 patients previously treated with troglitazone, supports the idea that the two agents have similar effects on glycemia and body weight.[76] The same study showed that pioglitazone is more effective than rosiglitazone in regard to LDL cholesterol and serum triglyceride levels. The difference between the effects of the drugs on lipids cannot be attributed to differences in their effects on serum free fatty acid concentrations, which decreased by similar amounts, approximately 20 to 30 percent.[30,33] Pioglitazone seems to act like a partial PPARα agonist in vitro, whereas rosiglitazone seems to be a pure PPARγ agonist.[77]

Data on mechanisms underlying the effects of the thiazolidinediones on lipids in humans are virtually nonexistent. For example, there are no data to characterize the effects of thiazolidinediones on the production and removal of lipoprotein parti-

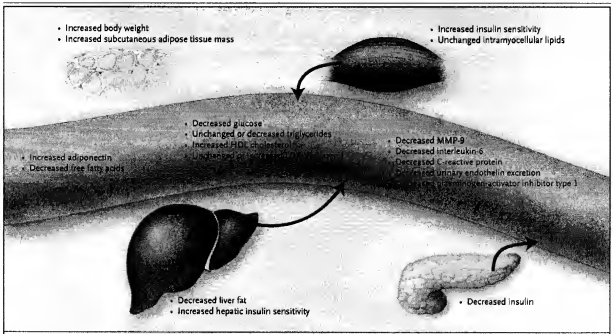

Figure 3. **Mechanism of Action of Thiazolidinediones in Vivo in Humans.**

Thiazolidinediones may keep fat where it belongs — that is, they may increase lipogenesis in adipose tissue, which decreases serum free fatty acid concentrations and increases subcutaneous adipose tissue mass and body weight. Adipose tissue expression and serum concentrations of adiponectin also increase, which, together with the lowering of serum free fatty acid levels, could contribute to increased hepatic insulin sensitivity, the lowering of hepatic fat content, and the inhibition of hepatic glucose production. The latter decreases plasma glucose concentrations. Serum insulin concentrations decrease as a consequence of enhanced insulin sensitivity and clearance. Thiazolidinediones have also been shown to decrease circulating or urinary markers of cardiovascular risk and vascular inflammation such as plasminogen-activator inhibitor type 1, C-reactive protein, matrix metalloproteinase 9 (MMP-9), and urinary endothelin excretion. HDL denotes high-density lipoprotein, and LDL low-density lipoprotein.

cles containing apolipoprotein A-I or apolipoprotein B. The cause of the increase in HDL and LDL cholesterol levels during rosiglitazone treatment is therefore unknown. The effects of rosiglitazone or pioglitzone on the size of LDL particles have not been studied in a double-blind, placebo-controlled trial. Rat and mouse models are not ideal for the study of human lipoprotein metabolism, because impaired clearance is the principal defect responsible for hypertriglyceridemia in these models, rather than overproduction of very-low-density lipoproteins, which is the case in humans.[78]

EFFECTS OF THIAZOLIDINEDIONES ON CONDITIONS CHARACTERIZED BY INSULIN RESISTANCE

Type 2 diabetes is currently the only approved indication for therapy with thiazolidinediones. However, thiazolidinediones have been tested as experimental therapies with variable success in other insulin-resistant conditions, such as nonalcoholic fatty liver disease,[79] polycystic ovary syndrome,[80] and lipodystrophies.[81]

NONALCOHOLIC FATTY LIVER DISEASE

Type 2 diabetes is strongly associated with nonalcoholic fatty liver disease, a spectrum of liver damage that ranges from benign hepatic steatosis to potentially fatal cirrhosis.[79] According to the third National Health and Nutrition Examination Survey, 6.4 million adults in the United States have nonalcoholic fatty liver disease.[82] It is the most common cause of levels of elevated levels of liver enzymes,[82] and elevated alanine aminotransferase levels predict type 2 diabetes independently of obesity.[83] Hepatic steatosis is associated with increased hepatic insulin resistance in humans[84] and correlates with insulin requirements during insulin therapy in patients with type 2 diabetes.[85]

Table 1. **Comparative Effects of Maximal Doses of Rosiglitazone (8 mg) and Pioglitazone (30 to 45 mg) on Glycemic Control as Measured by Absolute Change in Glycosylated Hemoglobin as Compared with Placebo or Control Group (Metformin, Sulfonylurea, or Insulin Alone or in Combination).**

Type of Therapy	Study	No. of Patients	Duration of Study	Decrease in Glycosylated Hemoglobin	Weight Gain*
			wk	%	*kg*
Pioglitazone					
Monotherapy	Aronoff et al.[17]	155	26	1.6	4.1
	Scherbaum and Göke[18]	162	26	0.7	1.9
	Rosenblatt et al.[19]	197	23	1.4	3.2
Combination therapy					
Metformin	Einhorn et al.[20]	328	16	0.8	2.3
Sulfonylurea	Kipnes et al.[21]	376	16	1.3	3.7
Insulin	Rosenstock et al.[22]	358	16	1.0	3.7
Rosiglitazone					
Monotherapy	Lebovitz et al.[23]	327	26	1.5	4.5
Combination therapy					
Metformin	Fonseca et al.[24]	223	26	1.2	3.1
	Gomez-Perez et al.[25]	70	26	1.5	3.3
Sulfonylurea	Vongthavaravat et al.[26]	348	26	1.2	—
Insulin	Raskin et al.[27]	207	26	1.3	4.4

* A dash indicates no data.

In several recent studies, thiazolidinediones have been shown to reduce fat accumulation in the liver in patients with type 2 diabetes[37,40-42] and in patients with lipodystrophy associated with the use of highly active antiretroviral therapy.[43] It is consistent with such findings that liver enzymes, which have been extensively monitored because of fear of hepatotoxicity, seem to decrease rather than increase during treatment with pioglitazone and rosiglitazone.[40,43]

Nonalcoholic steatohepatitis represents an advanced stage within the spectrum of nonalcoholic fatty liver disease and is defined histologically by the presence of steatosis along with areas of necrosis and inflammation. Recent studies have suggested that thiazolidinediones not only decrease liver fat content but also induce improvements in liver histology.[86,87]

POLYCYSTIC OVARY SYNDROME

The polycystic ovary syndrome is a disorder of unknown cause affecting approximately 4 percent of women of reproductive age.[88] Women with the polycystic ovary syndrome are frequently insulin resistant and at increased risk for type 2 diabetes.[89] The hyperinsulinemia accompanying insulin resistance is thought to contribute to hyperandrogenism in patients with the polycystic ovary syndrome.[80,90] Interventions that reduce insulin levels, such as weight loss and medications (e.g., metformin, diazoxide, or somatostatin analogues), decrease hyperandrogenism and reduce insulin resistance.[91] A large-scale placebo-controlled trial including 410 women showed that troglitazone treatment was associated with significant improvements in ovulatory function, hirsutism, hyperandrogenemia, and insulin resistance.[92] Similar data were recently reported in a small placebo-controlled study in which women underwent randomization to rosiglitazone and placebo or to rosiglitazone and clomiphene. Overall, 56 percent of women previously resistant to clomiphene ovulated: 33 percent of those who were treated with rosiglitazone alone and 77 percent of those who were treated with combination therapy.[93] Although metformin is considered safe for women who become pregnant, rosiglitazone and pioglitazone are classified as pregnancy category C owing to experimental evidence of growth retardation in mid-to-late gestation in animal models. Agents in category C have had toxic effects in studies in animal

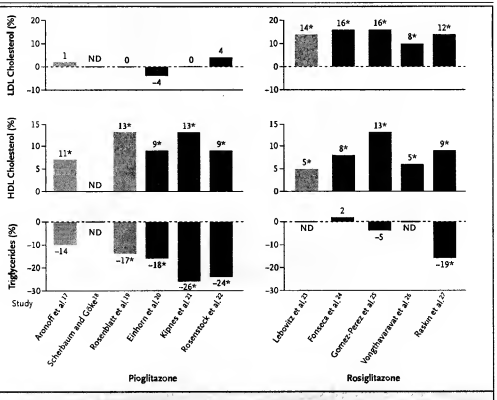

Figure 4. **Comparative Effects of Maximal Doses of Rosiglitazone (8 mg) and Pioglitazone (30 to 45 mg) on Serum Lipids and Lipoproteins in Randomized, Controlled Trials.**

All changes are shown as percent changes relative to the change in the placebo group (i.e., percent change from baseline with pioglitazone or rosiglitazone minus percent change with placebo from baseline). Asterisks indicate $P \leq 0.05$. LDL denotes low-density lipoprotein, HDL high-density lipoprotein, and ND no data. Yellow bars indicate monotherapy, red bars combination therapy with metformin, green bars combination therapy with sulfonylurea, and purple bars combination therapy with insulin.

models, but the results of studies in humans are inadequate; the agents should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Polycystic ovary syndrome is not an approved indication for the use of thiazolidinediones.

LIPODYSTROPHIES

By far the most common form of lipodystrophy is that associated with use of highly active antiretroviral therapy in patients with human immunodeficiency virus (HIV) disease. At least one lipodystrophy-related symptom develops after 12 to 18 months in approximately half of patients treated with highly active antiretroviral therapy.[94] Lipodystrophy, especially facial lipoatrophy, can be disfiguring and stigmatizing. There is no pharmacologic therapy for lipoatrophy, which is invariably accompanied by marked insulin resistance. Thiazolidinediones would seem to be an ideal therapy for insulin resistance and lipoatrophy associated with highly active antiretroviral therapy, because the drugs increase both insulin sensitivity and subcutaneous fat mass. However, in the only placebo-controlled trial in which patients with lipodystrophy associated with highly active antiretroviral therapy were treated (rosiglitazone, 8 mg per day for six months), there was no evidence of an increase in adiposity or body weight,[43] in contrast to studies in patients with type 2 diabetes.[30,32] In rare forms of human lipodystrophy, treatment with troglitazone for six months was reported to decrease glycosylated hemoglobin values and triglyceride levels and to induce a slight increase (2.4 percent) in subcutaneous fat.[95]

EFFECTS OF THIAZOLIDINEDIONES ON MARKERS OF CARDIOVASCULAR RISK

Cardiovascular disease is the leading cause of death worldwide and a major complication of type 2 diabetes.[96] In contrast to insulin, sulfonylureas, and metformin, all of which were shown in the United Kingdom Prospective Diabetes Study to be of benefit, or at least safe,[97,98] only data on markers of cardiovascular risk are currently available for thiazolidinediones.

BODY COMPOSITION AND BLOOD PRESSURE

Thiazolidinediones lead to an increase in body weight of 2 to 3 kg for every 1 percent decrease in glycosylated hemoglobin values (Table 1). The magnitude of the increase is similar during monotherapy and combination therapy with insulin[99] or metformin[20,24,25] in type 2 diabetes. The increase in body weight has been attributed to expansion of the subcutaneous fat depot, and in some patients to edema, whereas the mass of visceral fat remains unchanged[37] or decreases.[32] The clinical significance of these changes for patients with cardiovascular disease remains to be established. Systematic reviews of the literature have found no notable benefits of thiazolidinediones in regard to blood pressure.[100]

PLASMA AND URINARY MARKERS

Both pioglitazone and rosiglitazone may decrease the risk of cardiovascular disease by reducing glucose, insulin, and free fatty acid concentrations and by increasing HDL cholesterol levels. The significance of the increase in LDL cholesterol levels observed during rosiglitazone treatment is unclear, because of a lack of data on the effect of the drug on the size of LDL particles.

Circulating concentrations of adiponectin are low in patients with insulin-resistant conditions and are increased by thiazolidinediones. Circulating concentrations are also low in patients with coronary artery disease.[57,101]

Few data are available regarding the effects of thiazolidinediones on other markers of cardiovascular risk. One double-blind, placebo-controlled study showed that in patients with type 2 diabetes, rosiglitazone monotherapy was associated with a decrease in the ratio of urinary albumin to creatinine.[23] Another placebo-controlled study showed that rosiglitazone decreased plasma levels of plasminogen-activator inhibitor type 1 in cases of lipodystrophy associated with the use of highly active antiretroviral therapy in HIV-positive patients.[102] Other reports suggest that rosiglitazone decreases serum concentrations of the matrix-degrading MMP-9 (matrix metalloproteinase 9), C-reactive protein, and interleukin-6 (Fig. 3).[103,104]

VASCULAR FUNCTION AND DISEASE

Two double-blind, placebo-controlled studies have examined the effects of troglitazone on endothelium-dependent and -independent vasodilatation in humans. One study showed that eight weeks of troglitazone therapy had no effect on vascular function in patients with obesity,[34] whereas the other showed improvements in flow-mediated vasodilatation in a subgroup of patients in whom type 2 diabetes had been newly diagnosed.[105] A placebo-controlled study showed reduced progression of the intima–media thickness of the common carotid artery in patients with type 2 diabetes who were treated with rosiglitazone.[106] There are no data on the effects of thiazolidinediones on cardiovascular events in patients with insulin-resistant conditions. Two studies, the Prospective Pioglitazone Clinical Trial in Macrovascular Events and the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes trial, are currently investigating the effects of pioglitazone and rosiglitazone on cardiovascular events in patients with type 2 diabetes.[107]

SAFETY AND TOLERABILITY OF THIAZOLIDINEDIONES

WEIGHT GAIN, FLUID RETENTION, AND ANEMIA

The use of thiazolidinediones is associated with weight gain (Table 1), and a subgroup of patients have fluid retention and plasma volume expansion, which lead to peripheral edema. Edema has been reported in 4 to 6 percent of patients undergoing treatment with thiazolidinediones as compared with 1 to 2 percent of those receiving placebo or other hypoglycemic therapies. The increase in body weight and edema has been associated with an increase in the incidence of heart failure in patients being treated with thiazolidinediones and insulin. The Food and Drug Administration has included a warning in the prescription information for rosiglitazone (Avandia) and pioglitazone (Actos). The European Agency for the Evaluation of Me-

dicinal Products considers insulin therapy a contraindication to the use of thiazolidinediones. According to the agency, the frequency of congestive heart failure was 2.5 times as great with combination therapy with insulin and thiazolidinediones as with insulin alone, although the reason was not clear. The use of thiazolidinediones is also associated with slight decreases in the hemoglobin level and hematocrit, probably without clinical consequence.[100]

HEPATOTOXICITY

The idiosyncratic liver toxicity observed with troglitazone does not seem to be a class effect. In 13 double-blind studies, 1.91 percent of 2510 patients, 0.26 percent of 1526 patients, and 0.17 percent of 3503 patients receiving troglitazone, pioglitazone, and rosiglitazone had alanine aminotransferase values that were more than three times the upper limit of the reference range.[108] Alanine aminotransferase levels more than 10 times the upper limit of normal were observed in 0.68 percent of patients undergoing treatment with troglitazone as compared with none taking rosiglitazone and pioglitazone.

INSULIN SENSITIZATION BEYOND THIAZOLIDINEDIONES

The lipid-lowering and cardioprotective effects of PPARα agonists, such as fenofibrate[14] and gemfibrozil,[13] and the glucose-lowering effects of thiazolidinediones have led to a search for dual PPAR agonists (compounds with the combined effects of PPARα and PPARγ). Amelioration of insulin sensitivity in humans by means of interventions such as weight loss leads to the correction of abnormalities in both glucose and lipid metabolism. Therefore, dual PPAR agonists might be closer to true insulin sensitizers than are pure PPARγ agonists, which have only questionable effects on lipid metabolism. Studies in animal models suggest that this is the case.[109] According to the Food, Drug, and Cosmetic Act report of new drug applications, as many as eight dual PPAR agonists are currently under clinical development, including two in phase 3 trials.

Another approach to improving the metabolic profile of thiazolidinediones has been to identify selective PPAR modulators that act like partial agonists or antagonists of pure PPARγ agonists.[110] Examples of selective modulators that have been developed include tamoxifen and raloxifene, which act like antagonists in the breast but like estradiol in the bone.[111] Studies in animal models suggest that, unlike the thiazolidinedione full agonists, nonthiazolidinedione selective PPAR modulators have retained metabolic efficacy regarding the lowering of glucose and insulin concentrations but have counteracted weight gain and the expansion of subcutaneous adipose depots.[10] Clinical development of these agents has not yet begun. Finally, tyrosine-based nonthiazolidinedione PPARγ agonists, which are more potent than thiazolidinediones, have also been developed to surmount some of the problems of thiazolidinediones.[112]

CONCLUSIONS

The epidemic of type 2 diabetes has created a large need for new hypoglycemic therapies, but very few agents have been introduced during the past 20 years. The thiazolidinediones represent a potentially important new group of drugs with a mechanism of action differing from and perhaps complementary to existing therapies. Thiazolidinediones, unlike metformin or sulfonylureas, decrease hepatic fat content and increase insulin sensitivity in muscle. These properties would seem to make the drugs particularly useful in patients with insulin-resistant type 2 diabetes, but no data are currently available to help identify the patients who would respond best to these drugs. Although thiazolidinediones lower glucose concentrations and increase insulin sensitivity, their nonglycemic effects on body weight, lipids, and blood pressure have been a disappointment, implying that this class of medications will not reduce the need to treat dyslipidemia and hypertension with separate therapies.

Since cardiovascular disease is a major burden in patients with type 2 diabetes, data about the effects of thiazolidinediones on cardiovascular disease are urgently needed. Until such data are available, one might conclude that although the study of PPARs has greatly expanded our understanding of the biology of adipose tissue, currently available thiazolidinediones are no more than moderately effective and expensive alternatives to existing hypoglycemic therapies.

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About the Author
Anthony S. Fauci, MD, National Institute of Health, Betheseda, MD.
Eugene Braunwald, MD, Harvard Medical School, Boston, MA.
Dennis L. Kasper, MD, Harvard Medical School, Boston, MA.
Stephen L. Hauser, MD, University of California, San Francisco, CA.
Dan L. Longo, MD, National Institute of Health, Betheseda, MD.

trimester, treatment with adrenergic block_ agents should be [illegible]taken; when the fetus is of sufficient size, cesarean section may [illegible]llowed by extirpation of the tumor. Although the safety of adren[illegible] blocking drugs in pregnancy is not established, these agents have [illegible] administered in several cases without obvious adverse effect. [illegible]partum diagnosis and treatment lowers the maternal death rate to [illegible]ching nonpregnant pheochromocytoma patients; fetal death however, remains elevated.

[illegible]resectable and malignant tumors In cases of metastatic or [illegible]y invasive tumor in patients with intercurrent illness that pre[illegible] surgery, long-term medical management is required. When the [illegible]festations cannot be adequately controlled by adrenergic blocking [illegible]s, the concomitant administration of metyrosine may be required. [illegible] agent inhibits tyrosine hydroxylase, diminishes catecholamine [illegible]ction by the tumor, and often simplifies chronic management. [illegible]gnant pheochromocytoma frequently recurs in the retroperito[illegible], and it metastasizes most commonly to bone and lung. Although [illegible] malignant tumors are resistant to radiotherapy, combination [illegible]therapy has had limited success in controlling them. Use of ^{131}I-[illegible]BG has had limited success in the treatment of malignant pheo[illegible]cytoma, due to poor uptake of the radioligand.

[illegible]PROGNOSIS AND FOLLOW-UP The 5-year survival rate [illegible] surgery is usually over 95%, the recurrence rate is <10%. After [illegible]ful surgery, catecholamine excretion returns to normal in about [illegible]eks and should be measured to ensure complete tumor removal. [illegible]cholamine excretion should be assessed at the reappearance of [illegible]ive symptoms or yearly if the patient remains asymptomatic. [illegible] malignant pheochromocytoma, the 5-year survival rate is <50%. Complete removal cures the hypertension in approximately three-[illegible]s of patients. In the remainder, hypertension recurs but is usually [illegible] controlled by standard antihypertensive agents. In this group, ei[illegible] underlying essential hypertension or irreversible vascular damage [illegible] by catecholamines may cause the persistence of the hyperten[illegible].

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333 DIABETES MELLITUS

Alvin C. Powers

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Diabetes mellitus (DM) comprises a group of common metabolic disorders that share the phenotype of hyperglycemia. Several distinct types of DM exist and are caused by a complex interaction of genetics, environmental factors, and life-style choices. Depending on the etiology of the DM, factors contributing to hyperglycemia may include reduced insulin secretion, decreased glucose usage, and increased glucose production. The metabolic dysregulation associated with DM causes secondary pathophysiologic changes in multiple organ systems that impose a tremendous burden on the individual with diabetes and on the health care system. In the United States, DM is the leading cause of end-stage renal disease, nontraumatic lower extremity amputations, and adult blindness. With an increasing incidence worldwide, DM will likely continue to be a leading cause of morbidity and mortality for the foreseeable future.

CLASSIFICATION

Recent advances in the understanding of the etiology and pathogenesis of diabetes have led to a revised classification (Table 333-1). Although all forms of DM are characterized by hyperglycemia, the pathogenic mechanisms by which hyperglycemia arises differ widely. Some forms of DM are characterized by an absolute insulin deficiency or a genetic defect leading to defective insulin secretion, whereas other forms share insulin resistance as their underlying etiology. Recent changes in classification reflect an effort to classify DM on the basis of the pathogenic process that leads to hyperglycemia, as opposed to criteria such as age of onset or type of therapy (Fig. 333-1).

The two broad categories of DM are designated type 1 and type 2. Type 1A DM results from autoimmune beta cell destruction, which usually leads to insulin deficiency. Type 1B DM is also characterized by insulin deficiency as well as a tendency to develop ketosis. However, individuals with type 1B DM lack immunologic markers indicative of an autoimmune destructive process of the beta cells. The mechanisms leading to beta cell destruction in these patients are unknown. Relatively few patients with type 1 DM fall into the type 1B idiopathic category; many of these individuals are either African-American or Asian in heritage.

Type 2 DM is a heterogeneous group of disorders usually characterized by variable degrees of insulin resistance, impaired insulin secretion, and increased glucose production. Distinct genetic and metabolic defects in insulin action and/or secretion give rise to the common phenotype of hyperglycemia in type 2 DM (see below). The identification of distinct pathogenic processes in type 2 DM has important potential therapeutic implications, as pharmacologic agents that target specific metabolic derangements become available.

Two features of the current classification of DM diverge from previous classifications. First, the terms *insulin-dependent diabetes mellitus* (IDDM) and *noninsulin-dependent diabetes mellitus* (NIDDM)

Table 333-1 Etiologic Classification of Diabetes Mellitus

I. Type 1 diabetes (β-cell destruction, usually leading to absolute insulin deficiency)
   A. Immune-mediated
   B. Idiopathic
II. Type 2 diabetes (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly insulin secretory defect with insulin resistance)
III. Other specific types of diabetes
   A. Genetic defects of β-cell function characterized by mutations in:
      1. Hepatocyte nuclear transcription factor (HNF) 4α (MODY 1)
      2. Glucokinase (MODY 2)
      3. HNF-1α (MODY 3)
      4. Insulin promoter factor (IPF) 1 (MODY 4)
      5. HNF-1β (MODY 5)
      6. Mitochondrial DNA
      7. Proinsulin or insulin conversion
   B. Genetic defects in insulin action
      1. Type A insulin resistance
      2. Leprechaunism
      3. Rabson-Mendenhall syndrome
      4. Lipoatrophic diabetes
   C. Diseases of the exocrine pancreas—pancreatitis, pancreatectomy, neoplasm, cystic fibrosis, hemochromatosis, fibrocalculous pancreatopathy
   D. Endocrinopathies—acromegaly, Cushing's syndrome, glucagonoma, pheochromocytoma, hyperthyroidism, somatostatinoma, aldosteronoma
   E. Drug- or chemical-induced—Vacor, pentamidine, nicotinic acid, glucocorticoids, thyroid hormone, diazoxide, β-adrenergic agonists, thiazides, phenytoin, α-interferon, protease inhibitors, clozapine, beta blockers
   F. Infections—congenital rubella, cytomegalovirus, coxsackie
   G. Uncommon forms of immune-mediated diabetes—"stiff-man" syndrome, anti-insulin receptor antibodies
   H. Other genetic syndromes sometimes associated with diabetes—Down's syndrome, Klinefelter's syndrome, Turner's syndrome, Wolfram's syndrome, Friedreich's ataxia, Huntington's chorea, Laurence-Moon-Biedl syndrome, myotonic dystrophy, porphyria, Prader-Willi syndrome
IV. Gestational diabetes mellitus (GDM)

NOTE: MODY, maturity onset of diabetes of the young.
SOURCE: Adapted from American Diabetes Association, 2000

are obsolete. These previous designations reflected the observation that most individuals with type 1 DM (previously IDDM) have an absolute requirement for insulin treatment, whereas many individuals with type 2 DM (previously NIDDM) do not require insulin therapy to prevent ketoacidosis. However, because many individuals with type 2 DM eventually require insulin treatment for control of glycemia, the use of the latter term generated considerable confusion.

A second difference is that age is no longer used as a criterion in the new classification system. Although type 1 DM most commonly develops before the age of 30, an autoimmune beta cell destructive process can develop at any age. In fact, it is estimated that between 5 and 10% of individuals who develop DM after age 30 have type 1A DM. Likewise, although type 2 DM more typically develops with increasing age, it also occurs in children, particularly in obese adolescents.

OTHER TYPES OF DM Other etiologies for DM include specific genetic defects in insulin secretion or action, metabolic abnormalities that impair insulin secretion, and a host of conditions that impair glucose tolerance (Table 333-1). *Maturity onset diabetes of the young* (MODY) is a subtype of DM characterized by autosomal dominant inheritance, early onset of hyperglycemia, and impairment in insulin secretion (discussed below). Mutations in the insulin receptor cause a group of rare disorders characterized by severe insulin resistance.

DM can result from pancreatic exocrine disease when the majority of pancreatic islets (>80%) are destroyed. Several endocrinopathies can lead to DM as a result of excessive secretion of hormones that antagonize the action of insulin. Notable within this group are acromegaly and Cushing's disease, both of which may present with DM. Viral infections have been implicated in pancreatic islet destruction, but are an extremely rare cause of DM. Congenital rubella greatly increases the risk for DM; however, most of these individuals also have immunologic markers indicative of autoimmune beta cell destruction.

GESTATIONAL DIABETES MELLITUS (GDM) Glucose intolerance may develop and first become recognized during pregnancy. Insulin resistance related to the metabolic changes of late pregnancy increases insulin requirements and may lead to hyperglycemia or impaired glucose tolerance. GDM is seen in approximately 4% of pregnancies in the United States; most women revert to normal glucose tolerance post-partum but have a substantial risk (30 to 60%) of developing DM later in life.

EPIDEMIOLOGY

The worldwide prevalence of DM has risen dramatically over the past two decades. It is projected that the number of individuals with DM will continue to increase in the near future. Between 1976 and 1994, for example, the prevalence of DM among adults in the United States increased from 8.9% to 12.3%. These findings, based on national epidemiologic data, include individuals with a diagnosis of DM and those with undiagnosed DM (based on identical diagnostic criteria). Likewise, prevalence rates of impaired fasting glucose (IFG) increased from 6.5% to 9.7% over the same period. Although the prevalence of both type 1 and type 2 DM is increasing worldwide, the prevalence of type 2 DM is expected to rise more rapidly in the future because of increasing obesity and reduced activity levels.

There is considerable geographic variation in the incidence of both type 1 and type 2 DM. For example, Scandinavia has the highest rate of type 1 DM (in Finland, incidence is 35/100,000 per year). The

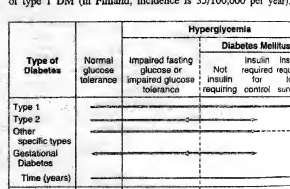

FIGURE 333-1 Spectrum of glucose homeostasis and diabetes. The spectrum from normal glucose tolerance to diabetes in type 1 diabetes, type 2 diabetes, other specific types of diabetes, and gestational diabetes is shown from left to right. In most types of diabetes, the individual traverses from normal glucose tolerance to impaired glucose tolerance to frank diabetes. Arrows indicate that changes in glucose tolerance may be bi-directional in some types of diabetes. For example, individuals with type 2 diabetes may return to the impaired glucose tolerance category with weight loss; in gestational diabetes, diabetes may revert to impaired glucose tolerance or even normal glucose tolerance after delivery. The fasting plasma glucose (FPG) and 2-h plasma glucose (PG), after a glucose challenge for the different categories of glucose tolerance, are shown at the lower part of the figure (as defined by recent consensus panels—see text). These values do not apply to the diagnosis of gestational diabetes. Some types of diabetes may or may not require insulin for survival, hence the dotted line. (Conventional units are used in the figure.) *(Adapted from American Diabetes Association: Clinical Practice Guidelines, 2000)*

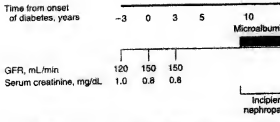

FIGURE 333-9 Time course of development of diabetic nephropathy. The relationship of time from onset of diabetes, the glomerular filtration rate (GFR), and the serum creatinine are shown. *(Adapted from DeFronzo RA, in Therapy for Diabetes Mellitus and Related Disorders, 1998)*

type 1 DM in the following respects: (1) microalbuminuria or overt nephropathy may be present when type 2 DM is diagnosed, reflecting its long asymptomatic period; (2) hypertension more commonly accompanies microalbuminuria or overt nephropathy in type 2 DM; and (3) microalbuminuria may be less predictive of progression to overt nephropathy in type 2 DM. Finally, it should be noted that albuminuria in type 2 DM may be secondary to factors unrelated to DM, such as hypertension, congestive heart failure, prostate disease, or infection.

Other renal problems may also occur in individuals with DM. Type IV renal tubular acidosis (hyporeninemic hypoaldosteronism) occurs in many individuals with DM. These individuals develop a propensity to hyperkalemia, which may be exacerbated by medications [especially angiotensin-converting enzyme (ACE) inhibitors]. Patients with DM are predisposed to radiocontrast-induced nephrotoxicity. Individuals with DM undergoing radiographic procedures with contrast dye should be well hydrated before and after dye exposure, and the serum creatinine should be monitored for several days following the procedure.

TREATMENT The optimal therapy for diabetic nephropathy is prevention. As part of comprehensive diabetes care, microalbuminuria should be detected at an early stage when effective therapies can be instituted. The recommended strategy for detecting microalbuminuria is outlined in Fig. 333-10. Interventions effective in slowing progression from microalbuminuria to overt nephropathy include: (1) near normalization of glycemia, (2) strict blood pressure control, and (3) administration of ACE inhibitors.

Improved glycemic control reduces the rate at which microalbuminuria appears and progresses in both type 1 and type 2 DM. However, once overt nephropathy exists, it is unclear whether improved glycemic control will slow progression of renal disease. During the phase of declining renal function, insulin requirements may fall as the kidney is a site of insulin degradation. Furthermore, glucose-lowering medications (sulfonylureas and metformin) may accumulate and are contraindicated in renal insufficiency.

Many individuals with type 1 or type 2 DM develop hypertension. Numerous studies in both type 1 and type 2 DM demonstrate the effectiveness of strict blood pressure control in reducing albumin excretion and slowing the decline in renal function. Blood pressure should be maintained at <130/85 mmHg in diabetic individuals without proteinuria. A slightly lower blood pressure (120/80) should be targeted for individuals with microalbuminuria or overt nephropathy. Treatment of hypertension is discussed below.

ACE inhibitors reduce the progression of overt nephropathy in individuals with type 1 or type 2 DM and should be prescribed in individuals with type 1 or type 2 DM and microalbuminuria. After 2 to 3 months of therapy, measurement of proteinuria should be repeated and the drug dose increased until either the albuminuria disappears or the maximum dose is reached. If an ACE inhibitor has an unacceptable side-effect profile (hyperkalemia, cough, and renal insufficiency), angiotensin II receptor blockers and calcium channel blockers (phenylalkylamine class) are alternatives. However, their efficacy in slowing the fall in glomerular filtration rate is not proven. Blood pressure control with any agent is extremely important, but a drug-specific benefit in diabetic nephropathy, independent of blood pressure control, has been shown only for ACE inhibitors.

A consensus panel of the American Diabetes Association (ADA) suggests modest restriction of protein intake in diabetic individuals with microalbuminuria (0.8 g/kg per day, which is the adult Recommended Daily Allowance, and about 10% of the daily caloric intake). Protein intake should be restricted further in individuals with overt diabetic nephropathy (0.6 g/kg per day), though conclusive proof of the efficacy of protein restriction is lacking.

Nephrology consultation should be considered after the diagnosis of early nephropathy. Once overt nephropathy ensues, the likelihood of ESRD is very high. As compared to nondiabetic individuals, hemodialysis in patients with DM is associated with more frequent complications, such as hypotension (autonomic neuropathy, loss of reflex tachycardia), more difficult vascular access, and accelerated progression of retinopathy. Survival after the onset of ESRD is shorter in the diabetic population compared to nondiabetics with similar clinical features. Atherosclerosis is the leading cause of death in diabetic individuals on dialysis, and hyperlipidemia should be aggressively treated. Renal transplantation from a living-related donor is the preferred therapy but requires chronic immunosuppression. Combined pancreas-kidney transplant offers the promise of normoglycemia but requires substantial expertise.

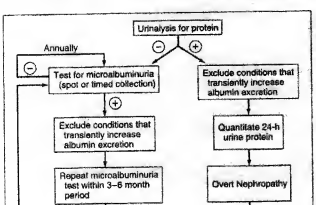

FIGURE 333-10 Screening for microalbuminuria. *(Adapted from DeFronzo RA, in Therapy for Diabetes Mellitus and Related Disorders, 1998)*

NEUROPATHY AND DIABETES MELLITUS

Diabetic neuropathy occurs in approximately 50% of individuals with long-standing type 1 and type 2 DM. It may manifest as polyneuropathy, mononeuropathy, and/or autonomic neuropathy. As with other complications of DM, the development of neuropathy correlates with the duration of diabetes and glycemic control. Because the clinical features of diabetic neuropathy are similar to those of other neuropathies, the diagnosis of *diabetic* neuropathy should be made only after other possible etiologies are excluded (Chap. 378).

Polyneuropathy/Mononeuropathy The most common form of diabetic neuropathy is distal symmetric *polyneuropathy*. It most frequently presents with distal sensory loss. Hyperesthesia, paresthesia, and pain also occur. Any combination of these symptoms may develop as neuropathy progresses. Physical examination reveals sensory loss, loss of ankle reflexes, and abnormal position sense. Paresthesia is characteristically perceived as a sensation of numbness, tingling, sharp-

ness, or burning that begins in the feet and spreads proximally. Neuropathic pain develops in some of these individuals, occasionally preceded by improvement in their glycemic control. Pain typically involves the lower extremities, is usually present at rest, and worsens at night. Both an acute (lasting <12 months) and a chronic form of painful diabetic neuropathy have been described. As diabetic neuropathy progresses, the pain subsides and eventually disappears, and a sensory deficit in the lower extremities persists.

Diabetic polyradiculopathy is a syndrome characterized by severe disabling pain in the distribution of one or more nerve roots. It may be accompanied by motor weakness. Intercostal or truncal radiculopathy causes pain over the thorax or abdomen. Involvement of the lumbar plexus or femoral nerve may cause pain in the thigh or hip and may be associated with muscle weakness in the hip flexors or extensors (diabetic amyotrophy). Fortunately, diabetic polyradiculopathies are usually self-limited and resolve over 6 to 12 months.

Mononeuropathy (dysfunction of isolated cranial or peripheral nerves) is less common than polyneuropathy in DM and presents with pain and motor weakness in the distribution of a single nerve. A vascular etiology is favored, but the pathogenesis is unknown. Involvement of the third cranial nerve is most common and is heralded by diplopia. Physical examination reveals ptosis and opthalmoplegia with normal papillary constriction to light. Sometimes cranial nerves IV, VI, or VII (Bell's palsy) are affected. Peripheral mononeuropathies or simultaneous involvement of more than one nerve (mononeuropathy multiplex) may also occur.

Autonomic Neuropathy Individuals with long-standing type 1 or 2 DM may develop signs of autonomic dysfunction involving the cholinergic, noradrenergic, and peptidergic (peptides such as pancreatic polypeptide, substance P, etc.) systems. DM-related autonomic neuropathy can involve multiple systems, including: the cardiovascular, gastrointestinal, genitourinary, sudomotor, and metabolic systems. Autonomic neuropathies affecting the cardiovascular system cause a resting tachycardia and orthostatic hypotension. Reports of sudden death have also been attributed to autonomic neuropathy. Gastroparesis and bladder-emptying abnormalities are also likely related to the autonomic neuropathy seen in DM (discussed below). Hyperhidrosis of the upper extremities and anhidrosis of the lower extremities result from sympathetic nervous system dysfunction. Anhidrosis of the feet can promote dry skin with cracking, which increases the risk of skin ulceration. Autonomic neuropathy may reduce counterregulatory hormone release, leading to an inability to sense hypoglycemia appropriately (*hypoglycemia unawareness*; Chap. 334), thereby subjecting the patient to the risk of severe hypoglycemia and complicating efforts to improve glycemic control.

℞ **TREATMENT** Treatment of diabetic neuropathy is less than satisfactory. Improved glycemic control should be pursued and will improve nerve conduction velocity, but the symptoms of diabetic neuropathy may not necessarily improve. Efforts to improve glycemic control may be confounded by autonomic neuropathy and hypoglycemia unawareness. Avoidance of neurotoxins (alcohol), supplementation with vitamins for possible deficiencies (B_{12}, B_6, folate; Chap. 75), and symptomatic treatment are the mainstays of therapy. Aldose reductase inhibitors do not currently offer significant symptomatic relief. Loss of sensation in the foot places the patient at risk for ulceration and its sequelae; consequently, prevention of such problems is of paramount importance. Since the pain of acute diabetic neuropathy may resolve over the first year, analgesics may be discontinued as progressive neuronal damage from DM occurs. Chronic, painful diabetic neuropathy is difficult to treat but may respond to tricyclic antidepressants (amitriptyline, desipramine, nortriptyline), gabapentin, nonsteroidal anti-inflammatory agents (avoid in renal dysfunction), and other agents (mexilitine, phenytoin, carbamazepine, capsaicin cream). Referral to a pain management center may be necessary.

Therapy of orthostatic hypotension secondary to autonomic neuropathy is difficult. A variety of agents have limited success (fludrocortisone, midodrine, clonidine, octreotide, and yohimbine) but have significant side effects. Nonpharmacologic maneuvers (adequate salt intake, avoidance of dehydration and diuretics, and lower extremity support hose) may offer some benefit.

GASTROINTESTINAL/GENITOURINARY DYSFUNCTION Long-standing type 1 and 2 DM may affect the motility and function of gastrointestinal (GI) and genitourinary systems. The most prominent GI symptoms are delayed gastric emptying (gastroparesis) and altered small- and large-bowel motility (constipation or diarrhea). *Gastroparesis* may present with symptoms of anorexia, nausea, vomiting, early satiety, and abdominal bloating. Nuclear medicine scintigraphy after ingestion of a radiolabeled meal is the best study to document delayed gastric emptying, but noninvasive "breath tests" following ingestion of a radiolabeled meal are under development. Though parasympathetic dysfunction secondary to chronic hyperglycemia is important in the development of gastroparesis, hyperglycemia itself also impairs gastric emptying. Nocturnal diarrhea, alternating with constipation, is a common feature of DM-related GI autonomic neuropathy. In type 1 DM, these symptoms should also prompt evaluation for celiac sprue because of its increased frequency. Esophageal dysfunction in long-standing DM is common but usually asymptomatic.

Diabetic autonomic neuropathy may lead to genitourinary dysfunction including cystopathy, erectile dysfunction, and female sexual dysfunction (reduced sexual desire, dyspareunia, reduced vaginal lubrication). Symptoms of diabetic cystopathy begin with an inability to sense a full bladder and a failure to void completely (Chap. 48). As sense a full bladder contractility worsens, bladder capacity and the postvoid residual increase, leading to symptoms of urinary hesitancy, decreased voiding frequency, incontinence, and recurrent urinary tract infections. Diagnostic evaluation includes cystometry and urodynamic studies.

Erectile dysfunction and retrograde ejaculation are very common in DM and may be one of the earliest signs of diabetic neuropathy. Erectile dysfunction, which increases in frequency with the age of the patient and the duration of diabetes, may occur in the absence of other signs of diabetic autonomic neuropathy.

℞ **TREATMENT** Current treatments for these complications of DM are inadequate. Improved glycemic control should be a primary goal, as some aspects (neuropathy, gastric function) may improve as near-normoglycemia is achieved. Smaller, more frequent meals that are easier to digest (liquid) and low in fat and fiber may minimize symptoms of gastroparesis. Cisapride (10 to 20 mg before each meal) is probably the most effective medication but has been removed from use in the U.S. market except under special circumstances. Other agents with some efficacy include dopamine agonists (metoclopramide, 5 to 10 mg, and domperidone, 10 to 20 mg, before each meal) and bethanechol (10 to 20 mg before each meal). Erythromycin interacts with the motilin receptor and may promote gastric emptying. Diabetic diarrhea in the absence of bacterial overgrowth is treated symptomatically with loperamide but may respond to clonidine at higher doses (0.6 mg tid) or octreotide (50 to 75 μg tid subcutaneously). Treatment of bacterial overgrowth with antibiotics is sometimes useful (Chap. 286).

Diabetic cystopathy should be treated with timed voiding or self-catheterization. Medications (bethanechol) are inconsistently effective. The drug of choice for erectile dysfunction is sildenafil, but the efficacy in individuals with DM is slightly lower than in the nondiabetic population (Chap. 51). Sexual dysfunction in women may be improved with use of vaginal lubricants, treatment of vaginal infections, and systemic or local estrogen replacement.

CARDIOVASCULAR MORBIDITY AND MORTALITY

Cardiovascular disease is increased in individuals with type 1 or type 2 DM. The Framingham Heart Study revealed a marked increase in several cardiovascular diseases in DM including peripheral vascular

may be warranted in diabetic individuals with any of the following: age ≥35 years, long-standing type 1 DM (>20 to 25 years' duration), microvascular complications of DM (retinopathy, microalbuminuria, or nephropathy), peripheral vascular disease, other risk factors of coronary artery disease, or autonomic neuropathy. Untreated proliferative retinopathy is a relative contraindication to vigorous exercise, since this may lead to vitreous hemorrhage or retinal detachment.

MONITORING THE LEVEL OF GLYCEMIC CONTROL Optimal monitoring of glycemic control involves plasma glucose measurements by the patient and an assessment of long-term control by the physician (measurement of HbA1c and review of the patient's self-measurements of plasma glucose). These measurements are complementary: the patient's measurements provide a picture of short-term glycemic control, whereas the HbA1c reflects average glycemic control over the previous 2 to 3 months. Integration of both measurements provides an accurate assessment of the glycemic control achieved.

Self-Monitoring of Blood Glucose Self-monitoring of blood glucose (SMBG) is the standard of care in diabetes management and allows the patient to monitor his or her blood glucose at any time. In SMBG, a small drop of blood and an easily detectable enzymatic reaction allow measurement of the capillary plasma glucose. By combining glucose measurements with diet history, medication changes, and exercise history, the physician and patient can improve the treatment program.

The frequency of SMBG measurements must be individualized and adapted to address the goals of diabetes care as defined by the patient and the health care provider. Individuals with type 1 DM should routinely measure their plasma glucose four to eight times per day to estimate and select mealtime boluses of short-acting insulin and to modify long-acting insulin doses. Most individuals with type 2 DM require less frequent monitoring, though the optimal frequency of SMBG has not been clearly defined. Individuals with type 2 DM who are on oral medications should utilize SMBG as a means of assessing the efficacy of their medication and diet. Since plasma glucose levels fluctuate less in these individuals, one to two SMBG measurements per day (or fewer) may be sufficient. Individuals with type 2 DM who are on insulin should utilize SMBG more frequently than those on oral agents.

Two devices for continuous blood glucose monitoring have been recently approved by the U.S. Food and Drug Administration (FDA). The Glucowatch uses iontophoresis to assess glucose in interstitial fluid, whereas the Minimed device uses an indwelling subcutaneous catheter to monitor interstitial fluid glucose. Both devices utilize immobilized glucose oxidase to generate electrons in response to changing glucose levels. Though clinical experience with these devices is limited, they perform well in clinical trials and appear to provide useful short-term information about the patterns of glucose changes as well as an enhanced ability to detect hypoglycemic episodes.

Although urine glucose testing does not provide an accurate assessment of glycemic control, urine ketones are a sensitive indicator of early diabetic ketoacidosis and should be measured in individuals with type 1 DM when the plasma glucose is consistently 16.7 mmol/L (300 mg/dL); during a concurrent illness; or with symptoms such as nausea, vomiting, or abdominal pain.

Assessment of Long-Term Glycemic Control Measurement of glycated hemoglobin is the standard method for assessing long-term glycemic control. When plasma glucose is consistently elevated, there is an increase in nonenzymatic glycation of hemoglobin; this alteration reflects the glycemic history over the previous 2 to 3 months, since erythrocytes have an average life span of 120 days. There are numerous laboratory methods for measuring the various forms of glycated hemoglobin, and these have significant interassay variations. Because of its superior specificity and reliability, the HbA1c assay performed by the high-performance liquid chromatography (HPLC) method has become the standard reference method for most glycated hemoglobin measurements. Since glycated hemoglobin measurements are usually compared to prior measurements, it is essential for the assay results to be comparable. Depending on the assay methodology for HbA1c, hemoglobinopathies, hemolytic anemia, and uremia may interfere with the HbA1c result.

Glycated hemoglobin or HbA1c should be measured in all individuals with DM during their initial evaluation and as part of their comprehensive diabetes care. As the primary predictor of long-term complications of DM, the HbA1c should mirror, to a certain extent, the short-term measurements of SMBG. These two measurements are complementary in that recent intercurrent illnesses may impact the SMBG measurements but not the HbA1c. Likewise, postprandial and nocturnal hyperglycemia may not be detected by the SMBG of fasting and preprandial capillary plasma glucose but will be reflected in the HbA1c. When measured by HPLC, the HbA1c approximates the following mean plasma glucose values: an HbA1c of 6% is 6.6 mmol/L (120 mg/dL), 7% is 8.3 mmol/L (150 mg/dL), 8% is 10.0 mmol/L (180 mg/dL), etc. [A 1% rise in the HbA1c translates into a 1.7-mmol/L (30 mg/dL) increase in the mean glucose.] The degree of glycation of other proteins, such as albumin, has been used as an alternative indicator of glycemic control when the HbA1c is inaccurate (hemolytic anemia, hemoglobinopathies). The fructosamine assay (using albumin) is an example of an alternative measurement of glycemic control and reflects the glycemic status over the 2 to 4 prior weeks. Current consensus statements do not favor the use of alternative assays of glycemic control, as there are no studies to indicate whether such assays accurately predict the complications of DM.

TREATMENT

Establishment of a Target Level of Glycemic Control Because the complications of DM are related to glycemic control, normoglycemia or near normoglycemia is the desired, but often elusive, goal for most patients. However, normalization of the plasma glucose for long periods of time is extremely difficult, as demonstrated by the DCCT. Regardless of the level of hyperglycemia, improvement in glycemic control will lower the risk of diabetes complications (Fig. 333-8).

The target for glycemic control (as reflected by the HbA1c) must be individualized, and the health care provider should establish the goals of therapy in consultation with the patient after considering a number of medical, social, and life-style issues. Some important factors to consider include the patient's age, ability to understand and implement a complex treatment regimen, presence and severity of complications of diabetes, ability to recognize hypoglycemic symptoms, presence of other medical conditions or treatments that might alter the response to therapy, life-style and occupation (e.g., possible consequences of experiencing hypoglycemia on the job), and level of support available from family and friends.

The ADA has established suggested glycemic goals based on the premise that glycemic control predicts development of DM-related complications. In general, the target HbA1c should be <7.0% (Table 333-9). Other consensus groups (such as the Veterans Administration) have suggested HbA1c goals that take into account the patient's life expectancy at the time of diagnosis and the presence of microvascular complications. Such recommendations strive to balance the financial and personal costs of glycemic therapy with anticipated benefits (reduced health care costs, reduced morbidity). One limitation to this approach is that the onset of hyperglycemia in type 2 DM is difficult to ascertain and likely predates the diagnosis. Furthermore, though the life expectancy can be predicted for a patient population, the physician must treat an individual patient; consequently, the target HbA1c must be individualized to accommodate these other considerations.

Type 1 Diabetes Mellitus • ***General aspects*** Comprehensive diabetes care should be instituted in all individuals with type 1 DM and should involve attention to nutrition, exercise, and risk factor management in addition to insulin administration. The ADA recommendations for fasting and bedtime glycemic goals and HbA1c targets are summarized in Table 333-9. The goal is to design and implement insulin regimens that mimic physiologic insulin secretion. Because in-

Table 333-9 Ideal Goals for Glycemic Control*

Index	Normal Range	Goal	Additional Action Suggested
Average preprandial glucose, mmol/L (mg/dL)	<5.5 (100)	4.4–6.7 (80–120)	<4.4 (80) *or* >7.8 (140)
Average bedtime glucose, mmol/L (mg/dL)	<6.1 (110)	5.5–7.8 (100–140)	<5.5 (100) *or* >8.8 (160)
HbA1c, %	<6	<7	>8

* These values are for whole blood measurements, and home glucose-monitoring devices may report either whole blood or plasma glucose values. Plasma glucose values are 10–15% higher than whole blood values. The upper limit of the HbA1c reference range is 6.0% (mean 5.0%, with a standard deviation of 0.5%). These goals must be individualized for each patient and must consider the patient's age and other medical conditions.

SOURCE: Adapted from American Diabetes Association, 2000.

quence of human insulin. Animal insulin (beef or pork) is no longer used. Human insulin has been formulated with distinctive pharmacokinetics to mimic physiologic insulin secretion (Table 333-11). In the United States, all insulin is formulated as U-100 (100 units/mL), whereas in some other countries it is available in other units (e.g., U-40 = 40 units/mL). One short-acting insulin formulation, lispro, is an insulin analogue in which the 28th and 29th amino acids (lysine and proline) on the insulin B chain have been reversed by recombinant DNA technology. This insulin analogue has full biologic activity but less tendency toward subcutaneous aggregation, resulting in more rapid absorption and onset of action and a shorter duration of action. These characteristics are particularly advantageous for allowing entrainment of insulin injection and action to rising plasma glucose levels following meals, although improvement in HbA1c values have not been found consistently. The shorter duration of action also appears to be associated with a decreased number of hypoglycemic episodes, primarily because the decay of lispro action corresponds better to the decline in plasma glucose after a meal. Insulin glargine is a long-acting biosynthetic human insulin that differs from normal insulin in that asparagine is replaced by glycine at amino acid 21, and two arginine residues are added to the C-terminus of the B chain. Compared to NPH insulin, the onset of insulin glargine action is later, the duration of action is longer (~24 h), and there is no pronounced peak. A lower incidence of hypoglycemia, especially at night, was reported in one trial with insulin glargine when compared to NPH insulin. Since glargine has only recently approved, clinical experience is limited. Additional insulin analogues are currently under development.

Basal insulin requirements are provided by intermediate (NPH or lente) or long-acting (ultralente or glargine) insulin formulations. These are usually combined with short-acting insulin in an attempt to mimic physiologic insulin release with meals. Although mixing of intermediate and short-acting insulin formulations is common practice, this mixing may alter the insulin absorption profile (especially those of short-acting insulins). For example, the absorption of regular insulin is delayed when mixed for even short periods of time (<5 min) with lente or ultralente insulin, but not when mixed with NPH insulin. Lispro absorption is delayed by mixing with NPH but not ultralente. Insulin glargine should not be mixed with other insulins. The miscibility of human regular and NPH insulin allows for the production of combination insulins that contain 75% NPH and 25% regular (75/25), 70% NPH and 30% regular (70/30), or equal mixtures of NPH and regular. These combinations of insulin are more convenient for the patient but prevent adjustment of only one component of the insulin formulation. The alteration in insulin absorption when the patient mixes different insulin formulation should not discourage the patient from mixing insulin. However, the following guidelines should be followed: (1) mix the different insulin formulations in the syringe immediately before injection (inject within 2 min after mixing); (2) if possible, do not store insulin as a mixture; and (3) follow the same routine in terms of insulin mixing and administration to standardize the physiologic response to injected insulin.

Insulin regimens Representations of the various insulin regimens that may be utilized in type 1 DM are illustrated in Fig. 333-12. Although the insulin profiles are depicted as "smooth," symmetric curves, there is considerable patient-to-patient variation in the peak and duration. In all regimens, long-acting insulins (NPH, lente, ultralente, or glargine insulin) supply basal insulin, whereas prandial insulin is provided by either regular or lispro insulin. Lispro should be injected just before a meal; regular insulin is given 30 to 45 min prior to a meal.

A shortcoming of current insulin regimens is that injected insulin immediately enters the systemic circulation, whereas endogenous in-

dividuals with type 1 DM lack endogenous insulin production, administration of basal, exogenous insulin is essential for regulating glycogen breakdown, gluconeogenesis, lipolysis, and ketogenesis. Likewise, postprandial insulin replacement should be appropriate for the carbohydrate intake and promote normal glucose utilization and storage.

Intensive management Intensive diabetes management is defined by the ADA as ". . . a mode of treatment for the person with DM that has the goal of achieving euglycemia or near-normal glycemia using all available resources to accomplish this goal." These resources include thorough and continuing patient education, comprehensive recording of plasma glucose measurements and nutrition intake by the patient, and a variable insulin regimen that matches glucose intake and insulin dose. Insulin regimens usually include multiple-component insulin regimens, multiple daily injections (MDI), or insulin infusion devices (all discussed below).

The benefits of intensive diabetes management and improved glycemic control include a reduction in the microvascular complications of DM and a possible delay or reduction in the macrovascular complications of DM. From a psychological standpoint, the patient experiences greater control over his or her diabetes and often notes an improved sense of well-being, greater flexibility in the timing and content of meals, and the capability to alter insulin dosing with exercise. In addition, intensive diabetes management in pregnancy reduces fetal malformation and morbidity. Intensive diabetes management is also strongly encouraged in newly diagnosed patients with type 1 DM because it may prolong the period of C-peptide production, which may result in better glycemic control and a reduced risk of serious hypoglycemia.

Although intensive management confers impressive benefits, it is also accompanied by significant personal and financial costs and is therefore not appropriate for all individuals. It requires a combination of dedication, persistence, and motivation on the part of the patient, as well as medical, educational, nursing, nutritional, and psychological expertise on the part of the diabetes management team. Circumstances in which intensive diabetes management should be strongly considered are listed in Table 333-10.

Insulin preparations Current insulin preparations are generated by recombinant DNA technology and consist of the amino acid se-

Table 333-10 Indications for Intensive Diabetes Management

- Otherwise healthy adults with either type 1 or type 2 diabetes (selected adolescents and older children)
- Purposeful, therapeutic attempt to avoid or lessen microvascular complications
- All pregnant women with diabetes; all women with diabetes who are planning pregnancy

Management of labile diabetes
Availability of health care professionals with appropriate expertise
Patients who have had kidney transplantation for diabetic nephropathy

SOURCE: Adapted from Farkas-Hirsch, 1998.

sulin is secreted into the portal vein. Thus, exogenous insulin administration exposes the liver to subphysiologic insulin levels. No insulin regimen reproduces the precise insulin secretory pattern of the pancreatic islet. However, the most physiologic regimens entail more frequent insulin injections, greater reliance on short-acting insulin, and more frequent capillary plasma glucose measurements. In general, individuals with type 1 DM require 0.5 to 1.0 U/kg per day of insulin divided into multiple doses. Initial insulin-dosing regimens should be conservative; approximately 40 to 50% of the insulin should be given as basal insulin. A single daily injection of insulin is not appropriate therapy in type 1 DM.

One commonly used regimen consists of twice-daily injections of an intermediate insulin (NPH or lente) mixed with a short-acting insulin before the morning and evening meal (Fig. 333-12*A*). Such regimens usually prescribe two-thirds of the total daily insulin dose in the morning (with about two-thirds given as intermediate-acting insulin and one-third as short-acting) and one-third before the evening meal (with approximately one-half given as intermediate-acting insulin and one-half as short-acting). The drawback to such a regimen is that it enforces a rigid schedule on the patient, in terms of daily activity and the content and timing of meals. Although it is simple and effective at avoiding severe hyperglycemia, it does not generate near-normal glycemic control in most individuals with type 1 DM. Moreover, if the patient's meal pattern or content varies or if physical activity is increased, hyperglycemia or hypoglycemia may result. Moving the intermediate insulin from before the evening meal to bedtime may avoid nocturnal hypoglycemia and provide more insulin as glucose levels rise in the early morning (so-called dawn phenomenon). The insulin dose in such regimens should be adjusted based on SMBG results with the following general assumptions: (1) the fasting glucose is primarily determined by the prior evening intermediate-acting insulin; (2) the pre-lunch glucose is a function of the morning short-acting insulin; (3) the pre-supper glucose is a function of the morning intermediate-acting insulin; and (4) the bedtime glucose is a function of the pre-supper, short-acting insulin.

Multiple-component insulin regimens refer to the combination of basal insulin; preprandial short-acting insulin; and changes in short-acting insulin doses to accommodate the results of frequent SMBG, anticipated food intake, and physical activity. Sometimes also referred to as *multiple daily injections*, such regimens offer the patient maximal flexibility in terms of life-style and the best chance for achieving near normoglycemia. One such regimen, shown in Fig. 333-12*B*, consists of a basal insulin with ultralente twice a day and preprandial lispro. The lispro dose is based on individualized algorithms that integrate the preprandial glucose and the anticipated carbohydrate intake. An alternative multiple-component insulin regimen consists of bedtime intermediate insulin, a small dose of intermediate insulin at breakfast (20 to 30% of bedtime dose), and preprandial short-acting insulin. There are numerous variations of these regimens that can be optimized for individual patients. Frequent SMBG (four to 8 times per day) is absolutely essential for these types of insulin regimens.

Continuous subcutaneous insulin infusion (CSII) is another multiple-component insulin regimen (Fig. 333-12*C*). Sophisticated insulin infusion devices are now available that can accurately deliver small doses of insulin (microliters per hour). For example, multiple basal infusion rates can be programmed to: (1) accommodate nocturnal versus daytime basal insulin requirement, (2) alter infusion rate during periods of exercise, or (3) select different waveforms of insulin infusion. A preprandial insulin ("bolus") is delivered by the insulin infusion device based on instructions from the patient, which follow individualized algorithms that account for preprandial plasma glucose and anticipated carbohydrate intake. These devices require a health professional with considerable experience with insulin infusion devices and very frequent patient interactions with the diabetes management team. Insulin infusion devices present unique challenges, such as infection at the infusion site, unexplained hyperglycemia because the infusion set becomes obstructed, or diabetic ketoacidosis if the pump becomes disconnected. Since most physicians use lispro insulin in CSII, the extremely short half-life of this insulin quickly leads to

Table 3. Pharmacokinetics of Insulin Preparations

Preparation	Time of Action			
	Onset, h	Peak, h	Effective Duration, h	Maximum Duration, h
Short-acting				
Lispro	<0.25	0.5–1.5	3–4	4–6
Regular	0.5–1.0	2–3	3–6	6–8
Intermediate-acting				
NPH	2–4	6–10	10–16	14–18
Lente	3–4	6–12	12–18	16–20
Long-acting				
Ultralente	6–10	10–16	18–20	20–24
Glargine	4	–[a]	24	>24
Combinations				
75/25–75% NPH, 25% regular	0.5–1	Dual	10–16	14–18
70/30–70% NPH, 30% regular	0.5–1	Dual	10–16	14–18
50/50–50% NPH, 50% regular	0.5–1	Dual	10–16	14–18

[a] Glargine has minimal peak activity.
SOURCE: Adapted from JS Skyler, in *Therapy for Diabetes Mellitus and Related Disorders*, 1998

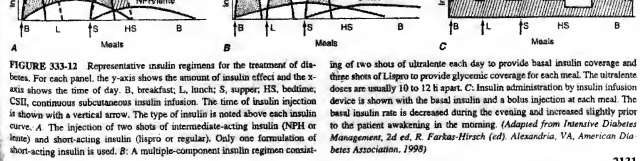

FIGURE 333-12 Representative insulin regimens for the treatment of diabetes. For each panel, the y-axis shows the amount of insulin effect and the x-axis shows the time of day. B, breakfast; L, lunch; S, supper; HS, bedtime; CSII, continuous subcutaneous insulin infusion. The time of insulin injection is shown with a vertical arrow. The type of insulin is noted above each insulin curve. *A*. The injection of two shots of intermediate-acting insulin (NPH or lente) and short-acting insulin (lispro or regular). Only one formulation of short-acting insulin is used. *B*: A multiple-component insulin regimen consisting of two shots of ultralente each day to provide basal insulin coverage and three shots of Lispro to provide glycemic coverage for each meal. The ultralente doses are usually 10 to 12 h apart. *C*: Insulin administration by insulin infusion device is shown with the basal insulin and a bolus injection at each meal. The basal insulin rate is decreased during the evening and increased slightly prior to the patient awakening in the morning. (*Adapted from Intensive Diabetes Management, 2d ed, R. Farkas-Hirsch (ed). Alexandria, VA, American Diabetes Association, 1998*)

insulin deficiency if the delivery system is interrupted. Essential to the safe use of infusion devices is thorough patient education about pump function and frequent SMBG.

Type 2 Diabetes Mellitus • ***General aspects*** The goals of therapy for type 2 DM are similar to those in type 1: improved glycemic control with near normalization of the HbA1c. While glycemic control tends to dominate the management of type 1 DM, the care of individuals with type 2 DM must also include attention to the treatment of conditions associated with type 2 DM (obesity, hypertension, dyslipidemia, cardiovascular disease) and detection/management of DM-related complications (Fig. 333-13). DM-specific complications may be present in up to 20 to 50% of individuals with newly diagnosed type 2 DM. Reduction in cardiovascular risk is of paramount importance as this is the leading cause of mortality in these individuals.

Diabetes management should begin with MNT (discussed above). An exercise regimen to increase insulin sensitivity and promote weight loss should also be instituted. After MNT and increased physical activity have been instituted, glycemic control should be reassessed; if the patient's glycemic target is not achieved after 3 to 4 weeks of MNT, pharmacologic therapy is indicated. Pharmacologic approaches to the management of type 2 DM include both oral glucose-lowering agents and insulin; most physicians and patients prefer oral glucose-lowering agents as the initial choice. Any therapy that improves glycemic control reduces "glucose toxicity" to the islet cells and improves endogenous insulin secretion.

Glucose-lowering agents Recent advances in the therapy of type 2 DM have generated considerable enthusiasm for oral glucose-lowering agents that target different pathophysiologic processes in type 2 DM. Based on their mechanisms of action, oral glucose-lowering agents are subdivided into agents that increase insulin secretion, reduce glucose production, or increase insulin sensitivity (Table 333-12). Oral glucose-lowering agents (with the exception of α-glucosidase inhibitors) are ineffective in type 1 DM and should not be used for glucose management of severely ill individuals with type 2 DM. Insulin is sometimes the initial glucose-lowering agent.

INSULIN SECRETAGOGUES Insulin secretagogues stimulate insulin secretion by interacting with the ATP-sensitive potassium channel on the beta cell (Fig. 333-1). These drugs are most effective in individuals with type 2 DM of relatively recent onset (<5 years), who have endogenous insulin production and tend to be obese. At maximum doses, first-generation sulfonylureas are similar in potency to second-generation agents but have a longer half-life, a greater incidence of hypoglycemia, and more frequent drug interactions (Table 333-13). Thus, second-generation sulfonylureas are generally preferred. An advantage to a more rapid onset of action is better coverage of the postprandial glucose rise, but the shorter half-life of such agents requires more than once-a-day dosing. Sulfonylureas reduce both fasting and postprandial glucose and should be initiated at low doses and increased at 1- to 2-week intervals based on SMBG. In general, sulfonylureas increase insulin acutely and thus should be taken shortly before a meal; with chronic therapy, though, the insulin release is more sustained. Repaglinide is not a sulfonylurea but also interacts with the ATP-sensitive potassium channel. Because of its short half-life, it is usually given with or immediately before each meal to reduce meal-related glucose excursions.

Insulin secretagogues are well tolerated in general. All of these agents, however, have the potential to cause profound and persistent hypoglycemia, especially in elderly individuals. Hypoglycemia is usually related to delayed meals, increased physical activity, alcohol intake, or renal insufficiency. Individuals who ingest an overdose of these agents develop prolonged and serious hypoglycemia and should be monitored closely in the hospital (Chap. 334). Most sulfonylureas are metabolized in the liver to compounds that are cleared by the kidney. Thus, their use in individuals with significant hepatic or renal dysfunction is not advisable. Weight gain, a common side effect of sulfonylurea therapy, results from the increased insulin levels and improvement in glycemic control. Some sulfonylureas have significant drug interactions with other medications such as alcohol, warfarin, aspirin, ketoconazole, α-glucosidase inhibitors, and fluconazole. Despite prior concerns that use of sulfonylureas might increase cardiovascular risk, recent trials have refuted this claim.

BIGUANIDES Metformin is representative of this class of agents. It reduces hepatic glucose production through an undefined mechanism and may improve peripheral glucose utilization slightly (Table 333-12). Metformin reduces fasting plasma glucose and insulin levels, improves the lipid profile, and promotes modest weight loss. The initial starting dose of 500 mg once or twice a day can be increased to 850 mg tid or 1000 mg bid. Because of its relatively slow onset of action and gastrointestinal symptoms with higher doses, the dose should be escalated every 2 to 3 weeks based on SMBG measurements. The major toxicity of metformin, lactic acidosis, can be prevented by careful patient selection. Metformin should not be used in patients with renal insufficiency [serum creatinine >133 μmol/L (1.5 mg/dL) in men or >124 μmol/L (1.4 mg/dL) in women, with adjustments for age], any form of acidosis, congestive heart failure, liver disease, or severe hypoxia. Metformin should be discontinued in patients who are seriously ill, in patients who can take nothing orally, and in those receiving radiographic contrast material. Insulin should be used until metformin can be restarted. Though well tolerated in general, some individuals develop gastrointestinal side effects (diarrhea, anorexia, nausea, and metallic taste) that can be minimized by gradual dose escalation. Because the drug is metabolized in the liver, it should not be used in patients with liver disease or heavy ethanol intake.

α-GLUCOSIDASE INHIBITORS α-Glucosidase inhibitors (acarbose and miglitol) reduce postprandial hyperglycemia by delaying glucose absorption; they do not affect glucose utilization or insulin secretion (Table 333-12). Postprandial hyperglycemia, secondary to impaired hepatic and peripheral glucose disposal, contributes significantly to the hyperglycemic state in type 2 DM. These drugs, taken just before each meal, reduce glucose absorption by inhibiting the enzyme that cleaves oligosaccharides into simple sugars in the intestinal lumen. Therapy should be initiated at a low dose (25 mg of acarbose or miglitol) with the evening meal and may be increased to a maximal dose over weeks to months (50 to 100 mg for acarbose or 50 mg for miglitol with each meal). The major side effects (diarrhea, flatulence, abdominal distention) are related to increased delivery of oligosaccharides to the large bowel and can be reduced somewhat by gradual upward dose titration. α-Glucosidase inhibitors may increase levels of sulfonylureas and increase the incidence of hypoglycemia. Simultaneous treatment with bile acid resins and antacids should be avoided. These agents should not be used in individuals with inflammatory bowel disease, gastroparesis, or a serum creatinine >177 μmol/L (2.0 mg/dL). This class of agents is not as potent as other oral agents in lowering the HbA1c but is unique in that it reduces the postprandial glucose rise even in individuals with type 1 DM.

THIAZOLIDINEDIONES Thiazolidinediones represent a new class of agents that reduce insulin resistance. These drugs bind to a nuclear receptor (peroxisome proliferator-activated receptor, PPAR-γ) that regulates gene transcription. The PPAR-γ receptor is found at highest

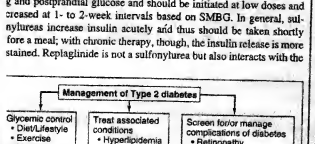

FIGURE 333-13 Essential elements in comprehensive diabetes care of type 2 diabetes.

Table 333-12 Oral Glucose-Lowering Therapies in T$_2$ DM

	Mechanism of Action	Examples	Anticipated Reduction in HbA1c, %	Agent-Specific Advantages	Agent-Specific Disadvantages	Contraindications
Insulin secretagogues	↑ Insulin		1–2			
Sulfonylureas		See Table 333-13		Lower fasting blood glucose	Hypoglycemia weight gain, hyperinsulinemia	Renal/liver disease
Meglitinide		Repaglinide		Short onset of action, lower postprandial glucose	Hypoglycemia	Liver disease
Biguanides	↓ Hepatic glucose production, weight loss, ↑ glucose utilization	Metformin	1–2	Weight loss, improved lipid profile, no hypoglycemia	Lactic acidosis, diarrhea, nausea, possible increased cardiovascular mortality	Serum creatinine >1.5 mg/dL (men), >1.4 mg/dL (women), radiographic contrast studies, seriously ill patients, acidosis
α-Glucosidase inhibitors	↓ Glucose absorption	Acarbose, miglitol	0.5–1.0	No risk of hypoglycemia	GI flatulence, ↑ liver function tests	Liver/renal disease
Thiazolidinediones	↓ Insulin resistance, ↑ glucose utilization	Rosiglitazone, pioglitazone	1–2	↓ Insulin and sulfonylurea requirements, ↓ triglycerides	Frequent hepatic monitoring for idiosyncratic hepatocellular injury (see text)	Liver disease, congestive heart failure
Medical nutrition therapy and physical activity	↓ Insulin resistance	Low-calorie, low-fat diet, exercise	1–2	Other health benefits	Compliance difficult, long-term success low	

levels in adipocytes but is expressed at lower levels in many other insulin-sensitive tissues. Agonists of this receptor promote adipocyte differentiation and may reduce insulin resistance in skeletal muscle indirectly. Thiazolidinediones reduce the fasting plasma glucose by improving peripheral glucose utilization and insulin sensitivity (Table 333-12). Circulating insulin levels decrease with use of the thiazolidinediones, indicating a reduction in insulin resistance. Although direct comparisons are not available, the two currently available thiazolidinediones appear to have similar efficacy; the therapeutic range for pioglitazone is 15 to 45 mg/d in a single daily dose and for rosiglitazone is 2 to 8 mg/d—once a day at lower doses and bid at higher doses. The ability of thiazolidinediones to influence other features of the insulin resistance syndrome is under investigation.

The prototype of this class of drugs, troglitazone, was withdrawn from the U.S. market after reports of hepatotoxicity and an association with an idiosyncratic liver reaction that sometimes led to hepatic failure. The two other thiazolidinediones, rosiglitazone and pioglitazone, thus far do not appear to induce the liver abnormalities seen with troglitazone. However, long-term experience with the newer agents is limited. Consequently, the FDA recommends measurement of liver function tests prior to initiating therapy with a thiazolidinedione and at regular intervals (every two months for the first year and then periodically). The thiazolidinediones raise LDL and HDL slightly and lower triglycerides by 10 to 15%, but the clinical significance of these changes is not known. Thiazolidinediones are associated with minor weight gain (1 to 2 kg), a small reduction in the hematocrit, and a mild increase in plasma volume. Cardiac function is not affected, but the incidence of peripheral edema is increased. They are contraindicated in patients with liver disease or congestive heart failure (class III or IV). Thiazolidinediones have been shown to induce ovulation in premenopausal women with polycystic ovary syndrome (see "Insulin Resistance Syndromes," above). Women should be warned about the risk of pregnancy, since the safety of thiazolidinediones in pregnancy is not established.

Table 333-13 Characteristics of Agents that Increase Insulin Secretion

Generic Name	Approved Daily Dosage Range, mg	Duration of Action, h	Clearance
Sulfonylurea			
First generation			
Chlorpropamide	100–500	>48	Renal
Tolazamide	100–1000	12–24	Hepatic, renal
Tolbutamide	500–3000	6–12	Hepatic
Second generation			
Glimepiride	1–8	24	Hepatic, renal
Glipizide	2.5–40	12–18	Hepatic
Glipizide (extended release)	5–10	24	Hepatic
Glyburide	1.25–20	12–24	Hepatic, renal
Glyburide (micronized)	0.75–12	12–24	Hepatic, renal
Meglitinide			
Repaglinide	0.5–16	2–6	Hepatic

SOURCE: Adapted from Zimmerman, 1998.

INSULIN THERAPY IN TYPE 2 DM Modest doses of insulin are quite efficacious in controlling hyperglycemia in newly diagnosed type 2 DM. Insulin should be considered as the initial therapy in type 2 DM, particularly in lean individuals or those with severe weight loss, in individuals with underlying renal or hepatic disease that precludes oral glucose-lowering agents, or in individuals who are hospitalized or acutely ill. Insulin therapy is ultimately required by a substantial number of individuals with type 2 DM because of the progressive nature of the disorder and the relative insulin deficiency that develops in patients with long-standing diabetes.

Because endogenous insulin secretion continues and is capable of providing some coverage of mealtime caloric intake, insulin is usually initiated in a single dose of intermediate-acting insulin (0.3 to 0.4 U/

kg per day), given either before breakfast or just before bedtime (or ultralente at bedtime). Since fasting hyperglycemia and increased hepatic glucose production are prominent features of type 2 DM, bedtime insulin is more effective in clinical trials than a single dose of morning insulin. Some physicians prefer a relatively low, fixed starting dose of intermediate-acting insulin (~15 to 20 units in the morning and 5 to 10 units at bedtime) to avoid hypoglycemia. The insulin dose may then be adjusted in 10% increments as dictated by SMBG results. Both morning and bedtime intermediate insulin may be used in combination with oral glucose-lowering agents (biguanides, α-glucosidase inhibitors, or thiazolidinediones).

CHOICE OF INITIAL GLUCOSE-LOWERING AGENT Though insulin is an effective primary therapy for type 2 DM, most patients and physicians currently prefer oral glucose-lowering drugs as the initial pharmacologic approach. The level of hyperglycemia should influence the initial choice of therapy. Assuming maximal benefit of MNT and increased physical activity has been realized, patients with mild to moderate hyperglycemia [fasting plasma glucose <11.1 to 13.9 mmol/L (200 to 250 mg/dL)] often respond well to a single oral glucose-lowering agent. Patients with more severe hyperglycemia [fasting plasma glucose >13.9 mmol/L (250 mg/dL)] may respond partially but are unlikely to achieve normoglycemia with oral monotherapy. Nevertheless, many physicians prefer a stepwise approach that starts with a single agent and adds a second agent to achieve the glycemic target (see "Combination Therapy," below). Some physicians begin insulin in individuals with severe hyperglycemia [fasting plasma glucose >13.9 to 16.7 mmol/L (250 to 300 mg/dL)]. This approach is based on the rationale that more rapid glycemic control will reduce "glucose toxicity" to the islet cells, improve endogenous insulin secretion, and possibly allow oral glucose-lowering agents to be more effective. If this occurs, the insulin may be discontinued.

Insulin secretagogues, biguanides, α-glucosidase inhibitors, thiazolidinediones, and insulin are approved for monotherapy of type 2 DM. Although each class of oral glucose-lowering agents has unique advantages and disadvantages, certain generalizations apply: (1) insulin secretagogues, biguanides, and thiazolidinediones improve glycemic control to a similar degree (1 to 2% reduction in HbA1c) and are more effective than α-glucosidase inhibitors; (2) assuming a similar degree of glycemic improvement, no clinical advantage to one class of drugs has been demonstrated, and any therapy that improves glycemic control is beneficial; (3) insulin secretagogues and α-glucosidase inhibitors begin to lower the plasma glucose immediately, whereas the glucose-lowering effects of the biguanides and thiazolidinediones are delayed by several weeks to months; (4) not all agents are effective in all individuals with type 2 DM (primary failure); (5) biguanides, α-glucosidase inhibitors, and thiazolidinediones do not directly cause hypoglycemia; and (6) most individuals will eventually require treatment with more than one class of oral glucose-lowering agents, reflecting the progressive nature of type 2 DM.

Considerable clinical experience exists with sulfonylureas and metformin because they have been available for several decades. It is assumed that the α-glucosidase inhibitors and thiazolidinediones, which are newer classes of oral glucose-lowering drugs, will reduce DM-related complications by improving glycemic control, although long-term data are not yet available. The thiazolidinediones are theoretically attractive because they targets a fundamental abnormality in type 2 DM, namely insulin resistance. However, these agents are currently more costly than others and require liver function monitoring.

A reasonable treatment algorithm for initial therapy proposes either a sulfonylurea or metformin as initial therapy because of their efficacy, known side-effect profile, and relatively low cost (Fig. 333-14). Metformin has the advantage that it promotes mild weight loss, lowers insulin levels, improves the lipid profile slightly, and may have a lower secondary failure rate. However, there is no difference in response rate or degree of glycemic control when metformin and

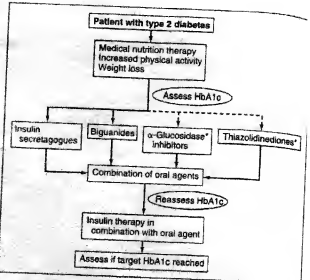

FIGURE 333-14 Glycemic management of type 2 diabetes. See text for discussion. *See text about use as monotherapy. The broken line indicates that biguanides or insulin secretagogues, but not α glucosidase inhibitors or thiazolidinediones, are preferred for initial therapy.

sulfonylureas are compared in randomized, prospective clinical trials. Based on SMBG results and the HbA1c, the dose of either the sulfonylurea or metformin should be increased until the glycemic target is achieved. α-Glucosidase inhibitors and thiazolidinediones are alternative, initial agents (Fig. 333-14).

When used as monotherapy, approximately one-third of individuals will reach their target glycemic goal with either a sulfonylurea or metformin. Approximately 25% of individuals will not respond to sulfonylureas or metformin; under these circumstances, the drug usually should be discontinued. Some individuals respond to one agent but not the other. The remaining individuals treated with either sulfonylureas or metformin alone will exhibit some improvement in glycemic control but will not achieve their glycemic target and should be considered for combination therapy.

COMBINATION THERAPY WITH GLUCOSE-LOWERING AGENTS A number of combinations of therapeutic agents are successful in type 2 DM, and the dosing of agents in combination is the same as when the agents are used alone. Because mechanisms of action of the first and second agents are different, the effect on glycemic control is usually additive. Commonly used regimens include: (1) insulin secretagogue with metformin or thiazolidinedione, (2) sulfonylurea with α-glucosidase inhibitor, and (3) insulin with metformin or thiazolidinedione. The combination of metformin and a thiazolidinedione is also effective and complementary. If adequate control is not achieved with two oral agents, bedtime insulin or a third oral agent may be added stepwise. However, long-term experience with any triple combination is lacking, and experience with two-drug combinations is relatively limited.

Insulin becomes required as type 2 DM enters the phase of relative insulin deficiency (as seen in long-standing DM) and is signaled by inadequate glycemic control on one or two oral glucose-lowering agents. Insulin can be used in combination with any of the oral agents in patients who fail to reach the glycemic target. For example, a single dose of intermediate-acting insulin at bedtime is effective in combination with metformin. As endogenous insulin production falls further, multiple injections of intermediate-acting and short-acting insulin regimens are necessary to control postprandial glucose excursions. These combination regimens are identical to the intermediate- and short-acting combination regimens discussed above for type 1 DM. Since the hyperglycemia of type 2 DM tends to be more "stable," these regimens can be increased in 10% increments every 2 to 3 days using SMBG

results. The daily insulin dose required can b : quite large (1 to 2 units/kg per day) as endogenous insulin pr...uction falls and insulin resistance persists. Individuals who require >1 unit/kg per day of intermediate-acting insulin should be considered for combination therapy with metformin or a thiazolidinedione. The addition of a thiazolidinedione can reduce insulin requirements in some individuals with type 2 DM, while maintaining or even improving glycemic control.

Intensive diabetes management (Table 333-10) is a treatment option in type 2 patients who cannot achieve optimal glycemic control and are capable of implementing such regimens. A recent study from the Veterans Administration found that intensive diabetes management is not associated with a greater degree of side effects (hypoglycemia, weight gain) than standard insulin therapy. The effects of higher insulin levels associated with intensive diabetes management on the prognosis of diseases commonly associated with type 2 DM (cardiovascular disease, hypertension) is still debated. In selected patients with type 2 DM, insulin pumps improve glycemic control and are well tolerated.

Emerging Therapies Whole pancreas transplantation (conventionally performed concomitantly with a renal transplant) may normalize glucose tolerance and is an important therapeutic option in type 1 diabetes, though it requires substantial expertise and is associated with the side effects of immunosuppression. Pancreatic islet transplantation has been plagued by limitations in pancreatic islet isolation and graft survival, but recent advances in specific immunomodulation have greatly improved the results. Islet transplantation is an area of active clinical investigation.

Advances in molecular biology and new insights into normal mechanisms of glucose homeostasis have led to a number of emerging therapies for diabetes and its complications. For example, glucagon-like peptide 1, a potent insulin secretagogue, may be efficacious in type 2 DM. Inhaled insulin and additional insulin analogues are in advanced stages of clinical trials. Aminoguanidine, an inhibitor of the formation of advanced glycosylation end products, and inhibitors of protein kinase C may reduce the complications of DM. Closed-loop pumps that infuse the appropriate amount of insulin in response to changing glucose levels are potentially feasible now that continuous glucose-monitoring technology has been developed.

COMPLICATIONS OF THERAPY FOR DIABETES MELLITUS

As with any therapy, the benefits of efforts directed towards glycemic control must be weighed against the risks of treatment. Side effects of intensive treatment include an increased frequency of serious hypoglycemia, weight gain, increased economic costs, and greater demands on the patient. In the DCCT, quality of life was very similar in the intensive therapy and standard therapy groups. The most serious complication of therapy for DM is hypoglycemia (Chap. 334). Weight gain occurs with most (insulin, insulin secretagogues, thiazolidinediones) but not all (metformin and α-glucosidase inhibitors) therapies that improve glycemic control due to the anabolic effects of insulin and the reduction in glucosuria. In the DCCT, individuals with the greatest weight gain exhibited increases in LDL cholesterol and triglycerides as well as increases in blood pressure (both systolic and diastolic) similar to those seen in individuals with type 2 DM and insulin resistance. These effects could increase the risk of cardiovascular disease in intensively managed patients. As discussed previously, improved glycemic control is sometimes accompanied by a transient worsening of diabetic retinopathy or neuropathy.

ONGOING ASPECTS OF COMPREHENSIVE DIABETES CARE

The morbidity and mortality of DM-related complications can be greatly reduced by timely and consistent surveillance procedures (Table 333-14). These screening procedures are indicated for all individuals with DM, but numerous studies have documented that most individuals with diabetes do not receive comprehensive diabetes care. Screening for dyslipidemia and hypertension should be performed annually. In addition to routine health maintenance, individuals with diabetes should also receive the pneumococcal and tetanus vaccines (at recommended intervals) and the influenza vaccine (annually).

Table 333-14 Guidelines for Ongoing Medical Care for Patients with Diabetes

- Self-monitoring of blood glucose (individualized frequency)
- HbA1c testing (2–4 times/year)
- Patient education in diabetes management (annual)
- Medical nutrition therapy and education (annual)
- Eye examination (annual)
- Foot examination (1–2 times/year by physician; daily by patient)
- Screening for diabetic nephropathy (annual; see Fig. 333-13)
- Blood pressure measurement (quarterly)
- Lipid profile (annual)

An annual comprehensive eye examination should be performed by a qualified optometrist or ophthalmologist. If abnormalities are detected, further evaluation and treatment require an ophthalmologist skilled in diabetes-related eye disease. Because many individuals with type 2 DM have had asymptomatic diabetes for several years before diagnosis, a consensus panel from the ADA recommends the following ophthalmologic examination schedule: (1) individuals with onset of DM at <29 years should have an initial eye examination within 3 to 5 years of diagnosis, (2) individuals with onset of DM at >30 years should have an initial eye examination at the time of diabetes diagnosis, and (3) women with DM who are contemplating pregnancy should have an eye examination prior to conception and during the first trimester.

An annual foot examination should: (1) assess blood flow, sensation, and nail care; (2) look for the presence of foot deformities such as hammer or claw toes and Charcot foot; and (3) identify sites of potential ulceration. Calluses and nail deformities should be treated by a podiatrist; the patient should be discouraged from self-care of even minor foot problems.

An annual microalbuminuria measurement is advised in individuals with type 1 or type 2 DM and no protein on a routine urinalysis (Fig. 333-10). If the urinalysis detects proteinuria, the amount of protein should be quantified by standard urine protein measurements. If the urinalysis was negative for protein in the past, microalbuminuria should be the annual screening examination. Routine urine protein measurements do not detect low levels of albumin excretion. Screening should commence 5 years after the onset of type 1 DM and at the time of onset of type 2 DM.

SPECIAL CONSIDERATIONS IN DIABETES MELLITUS

PSYCHOSOCIAL ASPECTS As with any chronic, debilitating disease, the individual with DM faces a series of challenges that affect all aspects of daily life. The individual with DM must accept that he or she may develop complications related to DM. Even with considerable effort, normoglycemia can be an elusive goal, and solutions to worsening glycemic control may not be easily identifiable. The patient should view him- or herself as an essential member of the diabetes care team and not as someone who is cared for by the diabetes team. Emotional stress may provoke a change in behavior so that individuals no longer adhere to a dietary, exercise, or therapeutic regimen. This can lead to the appearance of either hyper- or hypoglycemia. Depression and eating disorders (in women) are more common in individuals with type 1 or type 2 DM (Chap. 78).

MANAGEMENT IN THE HOSPITALIZED PATIENT Virtually all medical and surgical subspecialties may be involved in

CLINICAL THERAPEUTICS

Inhaled Insulin for Diabetes Mellitus

Graham T. McMahon, M.D., M.M.Sc., and Ronald A. Arky, M.D.

This Journal feature begins with a case vignette that includes a therapeutic recommendation. A discussion of the clinical problem and the mechanism of benefit of this form of therapy follows. Major clinical studies, the clinical use of this therapy, and potential adverse effects are reviewed. Relevant formal guidelines, if they exist, are presented. The article ends with the authors' clinical recommendations.

A 52-year-old man with an 8-year history of type 2 diabetes mellitus visits his primary care provider for advice. His glucometer readings at home have been high despite treatment with a sulfonylurea, a thiazolidinedione, and metformin at maximal doses. He has never smoked. His glycated hemoglobin value is 8.6% and his fasting blood glucose concentration ranges between 170 and 220 mg per deciliter (9.4 and 12.2 mmol per liter). His blood pressure, weight, and lipid profile are within recommended target ranges. The patient and his physician discuss therapeutic options and agree that insulin treatment should be initiated. The physician wonders whether the patient might benefit from inhaled insulin and refers him to an endocrinologist for evaluation.

THE CLINICAL PROBLEM

Diabetes mellitus, a major cause of illness and death across the globe, is responsible for a growing proportion of national health care expenditures. Insulin treatment is necessary for a substantial minority of patients with diabetes; more than 5 million Americans take insulin injections every day.[1-4] A wide range of subcutaneous insulins are available, many administered with penlike delivery devices and ultrafine needles that enhance the comfort and convenience of insulin treatment.[5] However, surveys indicate substantial resistance to insulin therapy on the part of both patients with type 2 diabetes who are not taking insulin and clinicians who care for such patients; the reasons for this resistance include anticipated pain, inconvenience, fear of hypoglycemia, and concern about weight gain.[6-8] True insulin and needle phobias are uncommon, although many patients appear to avoid insulin injections and blood glucose testing because of anxiety.[6,9-11] The youngest and oldest patients are least likely to accept injectable therapy and thus pose the greatest challenge for physicians who want to initiate insulin treatment.[12] Although resistance can be mitigated through education, efforts to develop oral, nasal, and inhaled formulations of insulin have been driven by the preference of patients to avoid subcutaneous injections.[13]

From the Division of Endocrinology, Diabetes, and Hypertension, Brigham and Women's Hospital, Boston. Address reprint requests to Dr. McMahon at the Division of Endocrinology, Diabetes, and Hypertension, Brigham and Women's Hospital, 221 Longwood Ave., RFB-2, Boston, MA 02115, or at gmcmahon@partners.org.

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PATHOPHYSIOLOGY AND EFFECT OF THERAPY

Insulin is lifesaving for patients with type 1 diabetes, a disease characterized by beta-cell failure and insulin deficiency. Type 2 diabetes, by contrast, is characterized by defects in both insulin secretion and insulin action, with insulin deficiency usually emerging later in the course of the disease. Insulin supplementation is often required to attain good glycemic control in type 2 diabetes and is typically initiated if the glycated hemoglobin level is not in the target range despite treatment with a combination of oral hypoglycemic agents.[14]

Most proteins and peptides used for systemic therapeutic purposes, including insulin, have high molecular weights and are hydrophilic; as a result, the only suitable means of administration has been injection.[15] However, inhalation devices can now facilitate delivery of drugs to the lungs. Since the lung is a large microvascular organ, molecules that are formulated to reach the alveoli can gain access to the systemic circulation.[15,16] Effective distribution in the lung requires particles that have an aerodynamic diameter between 1 and 5 μm.[15,16]

Many inhaled medications do not require a high degree of precision in dosing, and portable devices for inhaled drug delivery may be characterized by considerable dose-to-dose variation because of differences in inhalational flow rates. These devices are unsuitable for the administration of drugs such as insulin, for which dose consistency is critical.[17] The development of suitable inhalation devices has therefore been a limiting factor in the production of a reliable, clinically useful form of inhaled insulin.

So far, the only device for insulin inhalation that has been approved by the Food and Drug Administration (FDA) is an inhaler that delivers a dry-powder formulation of human insulin produced by means of recombinant DNA technology (Exubera, Pfizer). After oral inhalation of a single dose of human insulin by means of this device, approximately 40% of the dose reaches the deep lung, and 10% of the total dose is bioavailable.[18-20] The amount of drug that is delivered to the oropharynx or swallowed is unlikely to have a clinical effect.[20]

The interval between the administration of insulin and the onset of glucose-lowering activity is shorter with inhaled insulin (10 to 20 minutes) than with subcutaneously administered soluble (regular) human insulin and is similar to the interval with subcutaneously administered rapid-acting insulin analogues such as aspart, glulisine, and lispro. These pharmacokinetic features make inhaled insulin a suitable agent for preprandial administration. Its duration of action is between that of the rapidly acting insulin analogues and that of regular human insulin.[20-22]

CLINICAL EVIDENCE

Inhaled insulin has been compared with subcutaneous insulin regimens in patients with type 1 diabetes and in those with type 2 disease and has been compared with oral hypoglycemic agents in patients with type 2 diabetes.[23] All these trials were open label; most lasted for less than 6 months, and more than 90% of the participants were white.[23,24]

Among patients with type 1 or type 2 diabetes who received either a combination of neutral protamine Hagedorn (NPH) and regular insulin two to three times daily or a combination of ultralente each night and inhaled insulin before each meal, the glycated hemoglobin level at 6 months did not differ significantly between the two treatment groups. Patients who received ultralente and inhaled insulin had slightly lower rates of hypoglycemia.[25,26]

Adding thrice-daily inhaled insulin to existing oral therapy is generally more effective over a 12-to-24-week period than adding a second oral hypoglycemic drug taken once or twice a day.[27-29] However, as compared with oral agents for diabetes, inhaled insulin is consistently associated with a significantly higher incidence of hypoglycemic events.[23,27-30]

In clinical trials, patients have been generally more satisfied with inhaled insulin than with subcutaneous insulin.[25,26,31,32] Whether this outcome will be borne out in clinical practice remains to be determined.

CLINICAL USE

The FDA and the European Medicines Agency have both approved the Exubera inhalation delivery system for the preprandial treatment of patients with type 1 or 2 diabetes.[18,33] Therefore, most of the available information regarding the use of inhaled insulin is based on studies of this agent. Several other manufacturers have preparations of inhaled insulin that are being evaluated in clinical trials but have not yet been approved.

Because of its rapid onset of activity, inhaled insulin is suitable for preprandial but not for basal use. Patients with diabetes that is suboptimally controlled with the use of oral agents alone can usually be successfully treated at the outset by adding a single subcutaneous dose of either NPH or glargine insulin that is given before bedtime and titrated to a target fasting glucose level of approximately 100 mg per deciliter (5.5 mmol per liter).[34] Patients who comply with such an ap-

proach and whose glycated hemoglobin levels remain above target levels while they are receiving a basal insulin benefit from additional prandial insulin therapy. Preprandial insulins such as inhaled insulin are therefore most suitable for patients with glycated hemoglobin levels that remain elevated after fasting glucose levels have been controlled with a basal insulin.

Inhaled insulin therapy may be especially useful for patients with a true needle phobia and those with extensive cutaneous lipodystrophy at injection sites, although the incidence of the latter problem is declining.[6] Inhaled insulin is not approved for use in pregnant women, children, or adolescents.

Smoking is a contraindication to the use of inhaled insulin; active smoking significantly increases the rate and extent of insulin absorption.[35,36] In contrast, passive exposure to tobacco smoke in nonsmokers decreases the rate and extent of insulin absorption.[37] Clinicians should therefore exercise caution if they are prescribing inhaled insulin for patients who work or live in a smoky environment.

The use of inhaled insulin in patients with underlying lung disease such as asthma or chronic obstructive pulmonary disease is not recommended, since the absorption of insulin in these patients can be unpredictable, particularly when they are also using an inhaled bronchodilator.[37,38] A simple upper respiratory tract infection may be less problematic: according to the manufacturer of Exubera, an experimental rhinovirus infection did not change the absorption of inhaled insulin.[37] There are no data regarding the effect of more severe respiratory tract infections, such as pneumonia, on the absorption of inhaled insulin. Nevertheless, it is prudent for patients initiating treatment with inhaled insulin to be trained in the use and receive a supply of subcutaneous insulin for situations in which pulmonary absorption might not be reliable.

All candidates for inhaled insulin therapy should be taught how to check their glucose level before meals. They should also undergo spirometry, and the drug should not be used if the forced expiratory volume in 1 second (FEV_1) is below 70% of the predicted value. Measurement of the diffusing capacity for carbon monoxide is not mandatory but can provide a useful baseline for monitoring changes in pulmonary function over time.

With the Exubera inhalational device, the actuation of the dose and the inhalation are separated into two steps (see the video in the Supplementary Appendix, available with the full text of this article at www.nejm.org). When a dose of insulin is required, the patient extends the chamber and places a single blister of powdered insulin into a slot in the front of the device (Fig. 1). The patient creates a compressed volume of air by squeezing the pneumatic handle. Once the device is activated, the powder is released into a visible cloud, where it is suspended in a small volume of air that can be inhaled. A 5-second breath-hold allows the drug to settle in the lungs.

The dose of inhaled insulin is measured in milligrams rather than in units. The manufacturer's guidelines suggest that the initial estimate of the appropriate premeal dose should be 0.05 mg per kilogram of body weight. Thus, a person who weighs 100 kg should take 5 mg of inhaled insulin before each meal. However, unlike subcutaneous insulins, inhaled insulin is currently available in only two fixed doses (1 mg and 3 mg, approximately equivalent to 3 units and 8 units of insulin, respectively). Since only one blister can be used at each inhalation, multiple inhalations before each meal are necessary if the required dose of insulin is not exactly 1 mg or 3 mg. Furthermore, the received dose varies depending on the combination of blisters used. Consecutive inhalation of insulin from three blisters containing 1 mg of insulin apiece causes a 30 to 40% higher insulin exposure than inhalation of insulin from one blister containing 3 mg of insulin. Therefore, patients should not replace a single 3-mg dose with three consecutive 1-mg doses.[38]

Patient education regarding the use of inhaled insulin is critical to maximize the consistency of technique and dose delivery. Maintenance of the inhaler is also essential. The device must be cleaned weekly and allowed to air dry, since moisture in the chamber absorbs the insulin powder. In addition, an internal valve (included with each box of insulin blister packs) must be replaced every 2 weeks; this step requires manual dexterity.

Follow-up should include spirometry at 6 months and then every year because of the potential effect of inhaled insulin on pulmonary function. If the FEV_1 is confirmed to have declined by more than 20% or by more than 500 ml from the baseline value, inhaled insulin should be discontinued indefinitely.[39]

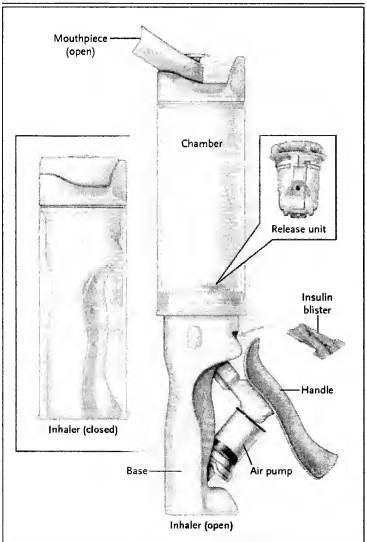

Figure 1. Inhaled Insulin Device.

The Exubera inhaled insulin device is closed for portability and opened before use. It is activated after insertion of an insulin blister. The release unit must be changed every 2 weeks.

Inhaled insulin is more expensive than other mealtime insulin. The average monthly cost of inhaled insulin in the amount recommended for a 100-kg patient is approximately $112.[40] In comparison, the average monthly wholesale cost for a similar dose of injectable insulin is $33 for regular insulin, $76 for a rapid-acting insulin analogue, and $102 for a rapid-acting insulin analogue in a penlike delivery device.[41] Many managed-care organizations offer limited coverage for inhaled insulin, placing it in a tier of medications that require preapproval, higher patient copayments, or both.[40]

ADVERSE EFFECTS

Two studies involving patients with type 1 diabetes and one study involving patients with type 2 diabetes showed a lower overall incidence of hypoglycemia among patients who received inhaled insulin than among those who received injected regular insulin.[25,26,42] However, two of these trials showed an increased incidence of severe hypoglycemia among the patients who received inhaled insulin.[26,42] The rate of hypoglycemia after the use of the Exubera device has not been compared with that associated with the alternative preprandial insulins (aspart, glulisine, or lispro) in head-to-head trials.

Diabetes is associated with abnormal lung function.[43,44] Inhaled insulin has small additional effects on both the diffusing capacity for carbon monoxide and the FEV_1, suggesting effects on the alveolar-capillary membrane and lung elastic recoil, respectively; it is not clear whether these effects are correlated. However, the FEV_1 declined by more than 15% from the baseline value in 1.3% of patients with type 1 diabetes who received inhaled insulin and in 5% of patients with type 2 diabetes who received inhaled insulin. This loss of lung function appeared to resolve within 6 weeks of discontinuation of inhaled insulin after up to 2 years of treatment.[39] It is not known whether these changes in pulmonary function can be predicted on the basis of cough or dyspnea; cough has frequently been reported in clinical trials of inhaled insulin.[25-27,42]

AREAS OF UNCERTAINTY

Insulin acts as a weak growth factor when it binds to the type 1 insulin-like growth factor receptor. Short-term studies in animals have not shown a substantial effect on cell-proliferation indexes in the alveolar or bronchiolar areas of the lung. The long-term effects of supraphysiologic doses of insulin in the human lung or on neoplastic lung tissue are unknown.

Insulin antibody levels rise progressively with the increased duration of exposure to inhaled insulin in patients with type 1 or type 2 diabetes.[25,26,42,45] These levels stabilize within 9 to 12 months after the start of treatment and decline but do not normalize after cessation of treatment.[37] Antibody levels are especially elevated among patients with type 1 diabetes, increasing by

more than a factor of 8 after 6 months of the use of inhaled insulin.[37] The frequency of severe hypoglycemia and the onset or duration of insulin activity have not been shown to be altered in the presence of insulin antibodies,[45] but further study is required to confirm that these antibodies do not act as a reservoir for delayed insulin release.

Studies have suggested that patients with diabetes are likely to prefer inhaled insulin over insulin injection,[31,32] in some cases by a ratio of 8:1.[46] It is not clear whether any increases in patient preference, acceptability, or satisfaction will be translated into increased compliance and improved glucose control. Managed-care companies and patients will need to decide whether they are willing to pay the additional price for this alternative insulin delivery system. Other inhaled insulin systems are in various stages of development and will need to be compared with the Exubera inhalation device. Finally, the longer-term safety and efficacy of this form of therapy have not yet been established.

GUIDELINES

In the United Kingdom, the National Institute for Health and Clinical Excellence recommends that inhaled insulin be prescribed only by diabetes specialists and for patients with needle phobia or severe problems at injection sites.[47] The German Institute for Quality and Efficiency in Health Care has concluded that inhaled insulin offered no additional benefit over subcutaneously administered insulin.[48] No guidelines for the use of inhaled insulin have been developed by expert groups or societies in the United States.

RECOMMENDATIONS

The patient described in the vignette presents with circumstances that are typical of many persons for whom insulin therapy is recommended. Although the concept of inhaled insulin is likely to be attractive to many such patients, we would first target the fasting glucose before introducing a preprandial insulin. After appropriate education and with the necessary support in place, we would begin treatment with a basal insulin given before sleep, adjusting the dose to achieve a mean fasting glucose level of approximately 100 mg per deciliter. Thus, we do not recommend the use of inhaled insulin in this patient. Should the patient later require preprandial insulin, the freedom from subcutaneous injection offered by inhaled insulin should be weighed against the necessity for multiple inhalations (sometimes at each dose), added cost, limited portability, risk of hypoglycemia, and unknown long-term adverse effects of this form of therapy.

No potential conflict of interest relevant to this article was reported.

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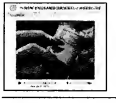

A video showing the use of inhaled insulin is available with the full text of this article at www.nejm.org.

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CLINICAL DECISIONS
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Management of Type 2 Diabetes

This interactive feature addresses the diagnosis or management of a clinical case. A case vignette is followed by specific clinical options, none of which can be considered either correct or incorrect. In short essays, experts in the field then argue for each of the options. In the online version of this feature, available at www.nejm.org, readers can participate in forming community opinion by choosing one of the options and, if they like, providing their reasons.

CASE VIGNETTE

A 55-year-old woman with type 2 diabetes, obesity, and hypertension has been under your care for the past 2 years. She has no history of microalbuminuria, retinopathy, or neuropathy. She has never had a cardiovascular event and reports no cardiac symptoms.

In the past, she has successfully lost weight (from 5 to 12 kg) on various diets but each time has regained all of the weight she lost. She tries to walk 30 minutes each day. She monitors her fasting glucose levels three times weekly using a personal glucometer, and her morning fasting glucose levels have ranged between 110 and 140 mg per deciliter (6.1 and 7.8 mmol liter). She has been receiving metformin (1000 mg twice a day) and glipizide (10 mg twice daily).

She has hypertension that is treated with hydrochlorothiazide (25 mg daily) and lisinopril (20 mg daily). She takes aspirin (81 mg daily) and simvastatin (20 mg daily). She notes that she consistently takes her medications.

She has a family history of cardiovascular disease with early stroke. On physical examination, her body-mass index (the weight in kilograms divided by the square of the height in meters) is 31. Her blood pressure is 128/78 mm Hg. Her general assessment, including cardiorespiratory, abdominal, and neurologic examinations, is normal.

Her glycated hemoglobin level is 8.1%, and her creatinine 0.9 mg per deciliter (80 mmol per liter). She has no microalbuminuria, and liver-function studies are normal. She seeks advice about the management of her diabetes.

Which one of the following treatment options, any one of which could be considered correct, would you find most appropriate for this patient? Base your choice on the published literature, your past experience, recent guidelines, and other sources of information, as appropriate.

1. **Add pioglitazone.**
2. **Add neutral protamine Hagedorn (NPH) insulin before bedtime.**
3. **Add exenatide twice daily.**

To aid in your decision making, each of these approaches to treatment is defended by an expert in the management of diabetes in the following short essays. Given your knowledge of the condition and the points made by the experts, which treatment approach would you choose? Make your choice on our Web site (www.nejm.org).

TREATMENT OPTION 1

Add Pioglitazone

Ronald B. Goldberg, M.D.

The case vignette illustrates a key therapeutic decision most physicians face when managing type 2 diabetes: namely, how to advance treatment in patients whose glycated hemoglobin levels remain above the target value despite dual oral antihyperglycemic therapy, such as with metformin and glipizide, as in this patient. Medications such as pioglitazone can delay the almost inevitable necessity of initiating the use of insulin in such patients. Furthermore, patients receiving a thiazolidinedione who later need insulin may have a better response to it than those not receiving a thiazolidinedione. However, there are no comparative data to determine what the optimal treatment should be when a patient does not have

a response to dual oral therapy. I believe the addition of pioglitazone is a rational next step.

Several short-term trials have examined the effects of thiazolidinedione treatment as an "add-on" therapy in patients with elevated glycated hemoglobin values who are already taking maximum doses of metformin and a sulfonylurea. Collectively, these studies demonstrate that the addition of a thiazolidinedione can lower the glycated hemoglobin level by as much as 2 percentage points. Three such studies compared the addition of a thiazolidinedione or insulin to the metformin–sulfonylurea treatment regimen of subjects with baseline glycated hemoglobin values of more than 9.0%.[1-3] These studies showed that a thiazolidinedione had an efficacy similar to that of insulin in lowering glycated hemoglobin levels. Together, the studies suggest that, as compared with treatment with insulin, treatment with pioglitazone is associated with a lower incidence of hypoglycemia, a similar amount of weight gain, and an increase in the high-density lipoprotein (HDL) cholesterol level. The expenses associated with the triple oral therapies that include a thiazolidinedione are greater than those of either insulin (70% NPH insulin and 30% regular insulin) or insulin glargine added to metformin–sulfonylurea.[2,3]

Pioglitazone is likely to have few side effects and can be taken once daily. The weight gain that typically accompanies its use (3–4 kg, on average) can be mitigated by intensifying medical nutrition therapy at the time of initiation. Since recent evidence suggests that the use of thiazolidinediones may reduce bone density, a bone-density scan may be appropriate, particularly for women who are already postmenopausal.

It is possible that the need for initiating insulin therapy is delayed by the addition of pioglitazone in patients whose diabetes is inadequately controlled with the use of metformin and sulfonylurea. One study, A Diabetes Outcome Progression Trial (ADOPT), showed that rosiglitazone, when used as initial monotherapy in patients with a recent diagnosis of type 2 diabetes, maintained glycemic targets for longer than did treatment with sulfonylurea or metformin and suggested that this might be due to a beneficial effect on beta-cell function. Though the addition of pioglitazone to a regimen of metformin and a sulfonylurea could be expected to have a durable effect on the maintenance of improved glycemic control, especially if administered soon after the glycated hemoglobin level begins to rise, longer-term studies are needed to evaluate the effectiveness of this approach.

In support of this strategy, the ratio of proinsulin to insulin, considered a marker of beta-cell function, improved when pioglitazone was added to metformin and sulfonylurea as treatment.[4] Pioglitazone also mobilizes fat from the liver, an effect that is thought to be accompanied by sensitization of the liver to insulin. Fatty liver is common in patients with diabetes and is linked in selected patients to the development of steatohepatitis, which pioglitazone has been shown to ameliorate.

Finally, despite the findings in meta-analyses that rosiglitazone may increase the risk of ischemic events, a similar effect has not been demonstrated for pioglitazone.[5] In fact, there is evidence that treatment with pioglitazone increases the HDL cholesterol level by 10 to 15%, lowers the systolic blood pressure by 4 to 5 mm Hg, and reduces the thickness of the carotid wall, as compared with a sulfonylurea. In addition, a marginally beneficial effect on ischemic events was found when pioglitazone was added to existing treatment in patients with type 2 diabetes in the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive), a randomized, double-blind, controlled clinical trial of a strategy that was considered cost-effective. In combination, these results support the possibility that pioglitazone may have cardioprotective effects; it would be my choice for this patient.

Dr. Goldberg reports receiving speaker's honoraria from both Takeda and GlaxoSmithKline and consulting fees and grant support from Takeda. No other potential conflict of interest relevant to this article was reported.

From the Division of Endocrinology, Diabetes, and Metabolism, Diabetes Research Institute, University of Miami Miller School of Medicine, Miami.

TREATMENT OPTION 2

Add NPH Insulin before Bedtime

Rury Holman, F.R.C.P.

The case vignette of a patient with type 2 diabetes who has suboptimal glycemic control despite receiving maximum-dose oral therapy with met-

formin and a sulfonylurea is all too familiar. It reflects the progressive nature of the condition, in which declining beta-cell function results in elevations in glycemia year after year[6] unless antidiabetes medications are added or the doses of these medications are increased. In this obese patient who has no clinical evidence of complications from diabetes and whose cardiovascular risk factors are currently well managed, the immediate concern is the need to reduce the glycated hemoglobin level to below that recommended in the International Diabetes Federation 2005 guidelines (6.5%) to minimize the risk of future complications. Ideally, glycemic control should be handled in a proactive manner, according to the joint consensus algorithm for the management of hyperglycemia from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD),[7] which suggests that a glycated hemoglobin value of 7% or more should serve as "a call to action to initiate or change therapy, with the goal of achieving a glycated hemoglobin level as close to the nondiabetic range as possible."

Adding a third oral agent is not recommended, given that the patient already has a glycated hemoglobin value of 8.1% and that this approach is relatively more expensive and potentially not as effective in reducing glycemia as adding insulin would be.[7] Adding a basal insulin to existing oral therapy has been shown to be more effective in reducing glycated hemoglobin levels than adding a thiazolidinedione — especially at higher initial glycated hemoglobin values — with less weight gain, no edema, salutary lipid changes, and a lower cost.[3] Indeed, the increased risk of edema, congestive heart failure, and fractures in women now recognized to be associated with thiazolidinediones and the uncertainty about their effects on the risk of cardiovascular disease have led to an updated recommendation by the ADA–EASD that greater caution should be exercised in their use. Adding exenatide in this patient would be unlikely to achieve the target glycated hemoglobin levels (<6.5% or <7.0%), given an expected absolute decrease in the level of only 0.5 to 1.0%, despite the potential weight loss, and would incur a risk of gastrointestinal side effects.[7] Also, exenatide requires twice-daily injections, and despite its increasing use, there have been no large-scale trials to assess its efficacy or safety in the long term.

Insulin therapy can reduce absolute glycated hemoglobin values sufficiently — by 1.5 to 3.5% — to allow glycemic targets to be met.[7] Adding an intermediate-acting insulin before bedtime is a relatively straightforward approach to increasing therapy for glycemia. It can be undertaken readily in a community-care–based setting and obviates the need to amend existing therapy. Some patients may be concerned about self-injection but can be reassured that with modern needles it is a virtually painless process and certainly much less onerous than their finger-stick capillary-glucose measurements. Maintaining existing sulfonylurea therapy when supplementing basal insulin requirements means that the required insulin dose is lower[8] and the problem of offsetting sudden glycemic deterioration when a sulfonylurea is withdrawn can be avoided.[9] The initiation of NPH insulin at bedtime involves a single injection at a time when patients will be undressed and does not require them to carry insulin-injection equipment during the day. Glycemic control can still be monitored, and the need for insulin-dose adjustments can be determined by continuing to measure mainly fasting glucose levels.

The Treat-to-Target trial showed that systematic titration of bedtime NPH insulin, used in addition to oral therapy, can safely achieve a 7% glycated hemoglobin value in a majority of overweight patients with type 2 diabetes who have glycated hemoglobin levels between 7.5% and 10.0% when receiving oral agents alone. The mean (±SE) weight gain was modest (2.8±0.2 kg) with a confirmed rate of hypoglycemic events of 5.1 per patient per year. The Treating to Target in Type 2 diabetes (4-T) trial showed that adding a basal insulin, instead of a biphasic insulin twice a day or a short-acting insulin three times a day, to metformin and sulfonylurea reduced the likelihood of hypoglycemia by half to three quarters, with a decrease in weight gain by half to two thirds. Insulin doses vary considerably among patients, but safe starting doses can be easily calculated, as shown in the 4-T trial. Patients can then adjust their doses, using a simple algorithm, as demonstrated in the Treat-to-Target trial. In the long term, this incremental approach to adding insulin therapy as a once-daily bedtime injection can ease the transition to a more complex insulin regimen in the face of continued hyperglycemic progression.

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From the University of Oxford, Diabetes Trials Unit, Oxford Centre for Diabetes, Endocrinology and Metabolism, Churchill Hospital, Oxford, United Kingdom.

TREATMENT OPTION 3

Add Exenatide Twice Daily

Daniel J. Drucker, M.D.

The management options for the treatment of type 2 diabetes have become more complex since the introduction of several new classes of drugs and emerging data about the safety and efficacy of older drugs. It remains difficult to predict the response to specific therapies targeting different antidiabetes mechanisms, and all three options posed in the case vignette are reasonable and efficacious. There are no available head-to-head trials that have directly compared the efficacies of pioglitazone, NPH insulin, and exenatide in patients in whom glycemic control has not been achieved with the use of metformin and a sulfonylurea; thus, it seems reasonable to make clinical decisions on the basis of available data. The addition of pioglitazone will improve insulin sensitivity and glucose control but probably will be associated with fluid retention and weight gain and an increased risk of osteoporosis.[10] Insulin therapy, while effective, may also be associated with weight gain and a need for more frequent glucose monitoring to minimize the risk of hypoglycemia.

Two new classes of antidiabetes agents based on the potentiation of incretin action have been approved for the treatment of type 2 diabetes: the glucagon-like peptide 1 (GLP-1) receptor agonists, exemplified by exenatide, and the dipeptidyl peptidase IV inhibitors that include sitagliptin and vildagliptin[11]; other drugs are currently in clinical trials. Exenatide (as well as GLP-1) lowers blood glucose levels by stimulating insulin secretion and inhibiting glucagon secretion. These drugs also appear to inhibit gastric emptying and enhance satiety, leading to weight loss in a substantial number of patients.

A recent meta-analysis of clinical trials involving incretin therapies concluded that the efficacy of these agents was generally similar to that of other antidiabetes therapies. Of direct relevance to the treatment of this patient, exenatide produces more potent control of postprandial glycemia than NPH insulin or pioglitazone, probably because exenatide suppresses gastric emptying. This finding may be important, in view of data linking the control of postprandial glycemia to cardiovascular risk in patients with diabetes. The opportunity to improve postprandial glucose control, while achieving weight loss, is appealing.

Although considerable preclinical data suggest that GLP-1–receptor agonists improve beta-cell function and are cardioprotective, such discussions may not be directly relevant for the care of this patient. The actions of GLP-1–receptor agonists on the stimulation of insulin and inhibition of glucagon secretion are glucose-dependent; hence, there is a very low risk of hypoglycemia in the absence of concomitant sulfonylurea therapy. The remarkable ability of GLP-1–receptor agonists to improve the glucose sensitivity of beta cells and potentiate insulin secretion rapidly suggests that discontinuation of the glipizide (or alternatively, the initial reduction of the dose by 50%), coincident with initiation of exenatide therapy, would be prudent.

The addition of exenatide to ongoing metformin and sulfonylurea therapy was associated with an absolute reduction of 0.8 to 1.0% in the glycated hemoglobin level, with 0.9 to 1.6 kg of weight loss, after 30 weeks of therapy in subjects with type 2 diabetes.[12] There have been several head-to-head comparisons of regimens of insulin administration, as compared with twice-daily exenatide, in patients who did not have adequate glycemic control when they were taking metformin and a sulfonylurea.[13,14] The use of exenatide and the use of insulin resulted in similar degrees of reduction in glycated hemoglobin and similar numbers of hypoglycemic events, but the resultant body weight was significantly higher at the end of the study in patients receiving insulin, often as much as 4 kg higher than in subjects taking exenatide.

What are the potential limitations associated with exenatide therapy? Gastrointestinal side effects, principally nausea, generally abate several weeks after the initiation of exenatide therapy.

Nausea and gastrointestinal upset may limit tolerability in 10 to 20% of patients, and pancreatitis has recently been described in subjects treated with exenatide, although the actual prevalence is low and the pathophysiological characteristics remain uncertain. Exenatide therapy is expensive, and its long-term durability and safety have not been defined. Since incretin drugs are new, they are comparatively more expensive than older agents, and we do not yet have outcome studies to determine the long-term effects of exenatide on beta-cell function or cardiovascular events. On the other hand, the use of exenatide reduces glycemia through multiple mechanisms of action, is simple to use, and provides superior control of postprandial glucose. Critically, unlike with existing diabetes therapies, many subjects will experience satiety and weight loss. These features make exenatide an appealing option for the treatment of patients in whom existing antidiabetic agents fail to achieve glycemic control.

Dr. Drucker reports receiving advisory or consulting fees from Amylin Pharmaceuticals, Arisaph Pharmaceuticals, Chugai, Conjuchem, Eli Lilly, Emisphere Technologies, GlaxoSmithKline, Glenmark Pharmaceuticals, Isis Pharmaceuticals, Merck Research Laboratories, Novartis Pharmaceuticals, Novo Nordisk, NPS Pharmaceuticals, Phenomix, Takeda, and Transition Pharmaceuticals; and grant support from Eli Lilly, Merck, and Novo Nordisk. No other potential conflict of interest relevant to this article was reported.

From Banting and Best Diabetes Centre, University of Toronto, Mount Sinai Hospital, Toronto.

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CORRECTION

Clinical Decisions: Management of Type 2 Diabetes; Treatment Option 3 — Add Exenatide Twice Daily

Clinical Decisions: Management of Type 2 Diabetes; Treatment Option 3 — Add Exenatide Twice Daily . The third sentence of the second paragraph (page 296) should have read "These drugs also appear to inhibit gastric emptying and enhance satiety, leading to weight loss in a substantial number of patients," rather than "These drugs also appear to enhance gastric emptying and satiety." The text has been corrected on the *Journal*'s Web site at www.nejm.org.

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Conditions & Treatments

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In type 1 diabetes, the body does not produce insulin, which is needed to take sugar (glucose) from the blood to the cells. You can learn more about these conditions and how to prevent them in this section. You will also find helpful information about insulin, diagnostic tests and tips on what to expect from your health care provider.

Hypoglycemia
Hypoglycemia, or low blood glucose, can happen even during those times when you're doing all you can to manage your diabetes.

Hyperglycemia
Hyperglycemia is a major cause of many of the complications that happen to people who have diabetes. For this reason, it's important to know what hyperglycemia is, what its symptoms are, and how to treat it.

Ketoacidosis
Ketoacidosis is a serious condition where the body has dangerously high levels of ketones -- or acids that build up in the blood -- and it can lead to diabetic coma (passing out for a long time) or even death.

Managing Your Blood Glucose
Keeping your blood glucose as close to normal as possible helps you feel better and reduces the risk of long-term complications of diabetes. Learn about checking your blood glucose, tight diabetes control, and an A1C test.

About Insulin and other drugs
In people with type 1 diabetes, the pancreas no longer makes insulin. The beta cells have been destroyed. They need insulin shots to use glucose from meals. Learn more about insulin and other drugs.

Insulin Pumps
Learn how you can use an insulin pump to help manage your diabetes.

Transplantation
Diabetes sometimes damages kidneys so badly that they no longer work. When kidneys fail, one option is a kidney transplant. There are also pancreas transplants, as well as islet cell transplants.

Related Conditions
Learn more about celiac disease, hemochromatosis and frozen shoulder, and how they relate to type 1 diabetes, in this section.

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About Insulin and other drugs

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Inside the pancreas, beta cells make the hormone insulin. With each meal, beta cells release insulin to help the body use or store the blood glucose it gets from

food. In people with type 1 diabetes, the pancreas no longer makes insulin. The beta cells have been destroyed and they need insulin shots to use glucose from meals. People with type 2 diabetes make insulin, but their bodies don't respond well to it. Some people with type 2 diabetes need diabetes pills or insulin shots

to help their bodies use glucose for energy. Insulin cannot be taken as a pill. The insulin would be broken down during digestion just like the protein in food. Insulin must be injected into the fat under your skin for it to get into your blood.

There are many different insulins for many different situations and lifestyles and there are more than 20 types of insulin sold in the United States. These insulins differ in how they are made, how they work in the body, and price. Insulin is made in labs to be identical to human insulin or it comes from animals (pigs). Future availability of animal insulin is uncertain.

The Basics of Insulin
Learn about insulin types, characteristics, strength, and additives.

Insulin Storage and Syringe Safety Information

Find out how you can safely dispose and reuse syringes, inject insulin, and store insulin.

Insulin Routines
You can find an insulin routine that will keep your blood glucose near normal, help you feel good, and fit your lifestyle.

New injectable drug recently approved by the FDA

Pramlintide (brand name **Symlin**) is a synthetic form of the hormone amylin, which is produced along with insulin by the beta cells in the pancreas. Amylin, insulin, and another hormone, glucagon, work in an interrelated fashion to maintain normal blood glucose levels.

Pramlintide injections taken with meals have been shown to modestly improve A1C levels without causing increased hypoglycemia or weight gain and even promoting modest weight loss. The primary side effect is nausea, which tends to improve over time and as an individual patient determines his or her optimal dose.

Because of differences in chemistry, pramlintide cannot be combined in the same vial or syringe with insulin and must be injected separately. Pramlintide has been approved for people with type 1 diabetes who are not achieving their goal A1C levels and for people with type 2 diabetes who are using insulin and are not achieving their A1C goals.

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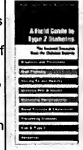
Type 2 Diabetes



Further Reading . . .
A Field Guide to Type 2 Diabetes is an excellent book for the patient or family member.

For more books on healthy living, click here.

Type 2 diabetes is the most common form of diabetes. In type 2 diabetes, either the body does not produce enough insulin or the cells ignore the insulin. Insulin is necessary for the body to be able to use glucose for energy. When you eat food, the body breaks down all of the sugars and starches into glucose, which is the basic fuel for the cells in the body. Insulin takes the sugar from the blood into the cells. When glucose builds up in the blood instead of going into cells, it can cause two problems:

- Right away, your cells may be starved for energy.
- Over time, high blood glucose levels may hurt your eyes, kidneys, nerves or heart.

Finding out you have diabetes is scary. But don't panic. Type 2 diabetes is serious, but people with diabetes can live long, healthy, happy lives.

While diabetes occurs in people of all ages and races, some groups have a higher risk for developing type 2 diabetes than others. Type 2 diabetes is more common in African Americans, Latinos, Native Americans, and Asian Americans/Pacific Islanders, as well as the aged population.

Conditions & Treatment

Arm yourself with information about conditions associated with type 2 diabetes, and how to prevent them. Conditions associated with type 2 diabetes include hyperglycemia and hypoglycemia. You will also find helpful information about insulin, oral medications, various diagnostic tests including the A1c test, managing and checking your blood glucose, and tips on what to expect from your health care provider.

Ask the Pharmacist - Online!

Diabetes Forecast - FREE ISSUE!

Information on Women and Diabetes

Information for recently diagnosed patients

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Complications
Having type 2 diabetes increases your risk for many serious complications. Some complications of type 2 diabetes include: heart disease (cardiovascular disease), blindness (retinopathy), nerve damage (neuropathy), and kidney damage (nephropathy). Learn more about these complications and how to cope with them.

Diabetes Learning Center for the Recently Diagnosed
You've just been diagnosed with diabetes. Chances are you have a million questions running through your head. To help you answer those questions, and take the first steps toward better diabetes care, visit the Diabetes Learning Center -- an area for people who are newly diagnosed with diabetes, or those needing basic information.

Your Body's Well Being
Make it a priority to take good care of your body. The time you spend now on eye care, foot care and skin care, as well as your heart health and oral health, could delay or prevent the onset of dangerous type 2 diabetes complications later in life. Plus, some of the best things you can do for your body are to stop smoking, and reduce the amount of alcohol you drink.

Common Concerns
This section addresses various areas to help you live with type 2 diabetes. What do you do when you're sick? What do you do when you travel? Can you get a flu shot with diabetes? How do you cope with having type 2 diabetes? Are you being discriminated against because you have diabetes? You'll find answers to these questions, and more in this section.

Ask the Pharmacist
The American Diabetes Association and Rite Aid "Ask the Pharmacist" area is where you can ask a pharmacist a question to help you manage your diabetes. Rite Aid and the ADA have partnered to allow you to access to Rite Aid's Drug Information Center from our Web site.

Women and Diabetes
Learn how to ensure your own health and well-being.

Health Information For Men
Learn how to ensure your own health and well-being.

Related Links

- Want to learn more about diabetes? Visit the Healthy Body Healthy Mind Web site and click on the link for "diabetes." Dr. Nathaniel Clark, Vice President of Clinical Affairs for the Association, and Dr. James Gavin, former president of the Association, joined other diabetes experts to share their insight on diabetes.

- Physician Recognition Program
  This Recognized Physician Directory helps individuals find doctors who have demonstrated they meet important standards of care.

- Education Recognition Program
  The following diabetes education programs in your area are Recognized by the American Diabetes Association. These Recognized programs meet the National Standards for excellence in diabetes education.

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Conditions & Treatments

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In type 2 diabetes, the body fails to properly use insulin, which is needed to take sugar from the blood to the cells. You can learn more about some conditions (including hyperglycemia and hypoglycemia) and how to prevent them in this section. You will also find helpful information about insulin, diagnostic tests and tips on what to expect from your health care provider.

Hypoglycemia
Hypoglycemia, or low blood sugar, can happen even during those times when you're doing all you can to control your diabetes.

Hyperglycemia
Hyperglycemia is a major cause of many of the complications that happen to people who have diabetes. For this reason, it's important to know what hyperglycemia is, what its symptoms are, and how to treat it.

What is Hyperosmolar Hyperglycemic Nonketotic Syndrome (HHNS)?
Hyperosmolar Hyperglycemic Nonketotic Syndrome, or HHNS, is a serious condition most frequently seen in older persons. HHNS can happen to people with either type 1 or type 2 diabetes, but it occurs more often in people with type 2.

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Other Medications for Type 2 Diabetes
The first treatment for type 2 diabetes is often meal planning for blood sugar control, weight loss, and exercising. Sometimes these measures are not enough to bring blood sugar down near the normal range. The next step is taking a medicine that lowers blood

glucose levels.

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Diabetes sometimes damages kidneys so badly that they no longer work. When kidneys fail, one option is a kidney transplant.

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About Insulin and other drugs

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Pramlintide injections taken with meals have been shown to modestly improve A1C levels without causing increased hypoglycemia or weight gain and even promoting modest weight loss. The primary side effect is nausea, which tends to improve over time and as an individual patient determines his or her optimal dose.

Because of differences in chemistry, pramlintide cannot be combined in the same vial or syringe with insulin and must be injected separately. Pramlintide has been approved for people with type 1 diabetes who are not achieving their goal A1C levels and for people with type 2 diabetes who are using insulin and are not achieving their A1C goals.

Other Diabetes Medications

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Ask the Pharmacist - Online!

Link for Life - Reduce your risk for heart attack and stroke

Find everything you need to know about Diabetes, from A to Z

Information for recently diagnosed patients

Find a recognized education program

The first treatment for type 2 diabetes is often meal planning for blood glucose (sugar) control, weight loss, and exercising. Sometimes these measures are not enough to bring blood glucose levels down near the normal range. The next step is taking a medicine that lowers blood glucose levels.

How they work

In people with diabetes, blood glucose levels are too high. These high levels occur because glucose remains in the blood rather than entering cells, where it belongs. But for glucose to pass into a cell, insulin must be present and the cell must be "hungry" for glucose.

People with type 1 diabetes don't make insulin. For them, insulin shots are the only way to keep blood glucose levels down.

People with type 2 diabetes tend to have two problems: they don't make quite enough insulin and the cells of their bodies don't seem to take in glucose as eagerly as they should.

All diabetes pills sold today in the United States are members of five classes of drugs: sulfonylureas, meglitinides, biguanides, thiazolidinediones, and alpha-glucosidase inhibitors. These five classes of drugs work in different ways to lower blood glucose levels.

Sulfonylureas

Sulfonylureas stimulate the beta cells of the pancreas to release more insulin. Sulfonylurea drugs have been in use since the 1950s. Chlorpropamide (brand name Diabinese) is the only first-generation sulfonylurea still in use today. The second generation sulfonylureas are used in smaller doses

Further Reading . . .

101 Medication Tips For People With Diabetes, 1st Edition is everything you need to know about medications and type 1, 2, or gestational diabetes in a easy-to-read Q & A format! For more books on healthy living with diabetes,

than the first-generation drugs. There are three second-generation drugs: glipizide (brand names Glucotrol and Glucotrol XL), glyburide (Micronase, Glynase, and Diabeta), and glimepiride (Amaryl). These drugs are generally taken one to two times a day, before meals. All sulfonylurea drugs have similar effects on blood glucose levels, but they differ in side effects, how often they are taken, and interactions with other drugs.

click here.

Meglitinides

Meglitinides are drugs that also stimulate the beta cells to release insulin. Repaglinide (brand name Prandin) and nateglinide (Starlix) are meglitinides. They are taken before each of three meals.

Because sulfonylureas and meglitinides stimulate the release of insulin, it is possible to have hypoglycemia (low blood glucose levels).

You should know that alcohol and some diabetes pills may not mix. Occasionally, chlorpropamide, and other sulfonylureas, can interact with alcohol to cause vomiting, flushing, or sickness. Ask your doctor if you are concerned about any of these side effects.

Biguanides

Metformin (brand name Glucophage) is a biguanide. Biguanides lower blood glucose levels primarily by decreasing the amount of glucose produced by the liver. Metformin also helps to lower blood glucose levels by making muscle tissue more sensitive to insulin so glucose can be absorbed. It is usually taken two times a day. A side effect of metformin may be diarrhea, but this is improved when the drug is taken with food.

Thiazolidinediones

Rosiglitazone (Avandia) and pioglitazone (ACTOS) are in a group of drugs called thiazolidinediones. These drugs help insulin work better in the muscle and fat and also reduce glucose production in the liver. The first drug in this group, troglitazone (Rezulin), was removed from the market because it caused serious liver problems in a small number of people. So far rosiglitazone and pioglitazone have not shown the same problems, but users are still monitored closely for liver problems as a precaution. Both drugs appear to increase the risk for heart failure in some individuals, and there is debate about whether rosiglitazone may contribute to an increased risk for heart attacks. Both drugs are effective at reducing A1C and generally have few side effects.

DPP-4 Inhibitors

A new class of medications called DPP-4 inhibitors help improve A1C without causing hypoglycemia. They

work by by preventing the breakdown of a naturally occuring compound in the body, GLP-1. GLP-1 reduces blood glucose levels in the body, but is broken down very quickly so it does not work well when injected as a drug itself. By interfering in the process that breaks down GLP-1, DPP-4 inhibitors allow it to remain active in the body longer, lowering blood glucose levels only when they are elevated. DPP-4 inhibitors do not tend to cause weight gain and tend to have a neutral or positive effect on cholesterol levels. Sitagliptin (Januvia) is currently the only DPP-4 inhibitor on the market.

Alpha-glucosidase inhibitors

Acarbose (brand name Precose) and meglitol (Glyset) are alpha-glucosidase inhibitors. These drugs help the body to lower blood glucose levels by blocking the breakdown of starches, such as bread, potatoes, and pasta in the intestine. They also slow the breakdown of some sugars, such as table sugar. Their action slows the rise in blood glucose levels after a meal. They should be taken with the first bite of a meal. These drugs may have side effects, including gas and diarrhea.

Oral combination therapy

Because the drugs listed above act in different ways to lower blood glucose levels, they may be used together. For example, a biguanide and a sulfonylurea may be used together. Many combinations can be used. Though taking more than one drug can be more costly and can increase the risk of side effects, combining oral medications can improve blood glucose control when taking only a single pill does not have the desired effects. Switching from one single pill to another is not as effective as adding another type of diabetes medicine.

Can diabetes pills help me?

Only people with type 2 diabetes can use pills to manage their diabetes. These pills work best when used with meal planning and exercise. This way you have three therapies working together to lower your blood glucose levels.

Diabetes pills don't work for everyone. Although most people find that their blood glucose levels go down when they begin taking pills, their blood glucose levels may not go near the normal range.

What are the chances that diabetes pills will work for you? Your chances are low if you have had diabetes for more than 10 years or already take more than 20 units of insulin each day. On the other hand, your chances are good if you developed diabetes recently or have needed little or no insulin to keep your blood glucose levels near normal.

Diabetes pills sometimes stop working after a few

months or years. The cause is often unknown. This doesn't mean your diabetes is worse. When this happens, oral combination therapy can help.

Even if diabetes pills do bring your blood glucose levels near the normal range, you may still need to take insulin if you have a severe infection or need surgery. Pills may not be able to control blood glucose levels during these stressful times when blood glucose levels shoot up.

Also, if you plan to become pregnant, you will need to control your diabetes with diet and exercise or with insulin. It is not safe for pregnant women to take oral diabetes medications.

There is no "best" pill or treatment for type 2 diabetes. You may need to try more than one type of pill, combination of pills, or pills plus insulin.

What about insulin?

Although it is a common practice to try pills before insulin, you may start on insulin based on several factors.

These factors include:

- how long you have had diabetes
- how high your blood glucose level is
- what other medicines you take
- your overall health

Because diabetes pills seem to help the body use insulin better, some people take them along with insulin shots. The idea behind this "combination" therapy is to try to help insulin work better.

Using diabetes medications wisely

In general, diabetes pills are safe and work well. But like any other drug, they must be used with care.

All diabetes pills can interact with other medicines. Because of the chance of medication interactions, you need to tell your doctor about all medicines you are taking. While you're taking diabetes pills, you should check with your doctor even before starting anything new -- even over-the-counter items.

Any sulfonylurea or meglitinide can cause blood glucose levels to drop too low (hypoglycemia). Metformin or the glitazones rarely cause hypoglycemia unless taken with insulin stimulators (sulfonylureas or repaglinide) or insulin injections. Acarbose or meglitol, taken as prescribed, does not cause hypoglycemia. However, hypoglycemia can occur when acarbose or meglitol is taken in combination with other oral diabetes medications.

Two new injectable drugs have recently been approved by the FDA

appropriate dose, if necessary. (Caution: some extended-release drugs will not work properly if they are cut into pieces; check with your pharmacist or doctor before using a pill splitter.)

Diabetes pills aren't perfect, but they can help to lower glucose levels for many people with type 2 diabetes. Keeping your blood glucose levels close to normal will help to reduce your risks for the long-term complications in the future and help you feel your best today.

Pramlintide (brand name **Symlin**) is a synthetic form of the hormone amylin, which is produced along with insulin by the beta cells in the pancreas. Amylin, insulin, and another hormone, glucagon, work in an interrelated fashion to maintain normal blood glucose levels.

Pramlintide injections taken with meals have been shown to modestly improve A1C levels without causing increased hypoglycemia or weight gain and even promoting modest weight loss. The primary side effect is nausea, which tends to improve over time and as an individual patient determines his or her optimal dose.

Because of differences in chemistry, pramlintide cannot be combined in the same vial or syringe with insulin and must be injected separately. Pramlintide has been approved for people with type 1 diabetes who are not achieving their goal A1C levels and for people with type 2 diabetes who are using insulin and are not achieving their A1C goals.

Exenatide (brand name **Byetta**) is the first in a new class of drugs for the treatment of type 2 diabetes called incretin mimetics. Exenatide is a synthetic version of exendin-4, a naturally-occurring hormone that was first isolated from the saliva of the lizard known as a Gila monster. Exenatide works to lower blood glucose levels primarily by increasing insulin secretion. Because it only has this effect in the presence of elevated blood glucose levels, it does not tend to increase the risk of hypoglycemia on its own, although hypoglycemia can occur if taken in conjunction with a sulfonylurea. The primary side effect is nausea, which tends to improve over time.

Like pramlintide, exenatide is injected with meals and, as with pramlintide, patients using exenatide have generally experienced modest weight loss as well as improved glycemic control. Exenatide has been approved for use by people with type 2 diabetes who have not achieved their target A1C levels using metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea.

The cost of care

Costs vary widely among the different medications. Even the same medication can vary in price from store to store. Call around to find the best price for the one you take.

Generic versions of some sulfonylureas are available. These cost less than brand-name products and in general are reliable. There is now a generic Metformin (brand name Glucophage).

To save you more money, ask your doctor to prescribe the largest tablet strength suitable for the dose you need. One 500-mg tablet, for example, often costs much less than two 250-mg tablets. You can then use a pill splitter (available at any pharmacy) to cut the larger tablet into halves or quarters to get the